Alfred Bader fonds

Correspondence

S

QUEEN'S UNIVERSITY ARCHIVES

LOCATOR 5095.5

BOX 6

FILE 4

Address: 20 St. James Street, Hammersmith, London, W6 9RW, UK
Telephone: +44 (0)20 8741 2305 **Fax**: +44 (0)20 8741 2307 **E-mail**: info@science-projects.org **Websites**: www.science-projects.org
www.the-observatory.org

SCIENCE
PROJECTS

Vat No 524009383. Registered Charity No 298542. Company limited by Guarantee No 2186073.

19 August 2005

Dr. Alfred Bader
924 East Juneau Avenue
Astor Hotel – Suite 622
Milwaukee WI 53202
USA

Dear Dr. Bader,

Thank you for your kind contribution towards the rent for the Observatory buildings. Your contribution has made all the difference in transforming our venture into a going concern. The fact we could demonstrate that we had secured revenue funding was the key factor in obtaining grants to renovate the buildings and restore the telescopes to bring the Equatorial Group site back to life.

I gather that the celebrations of the first ten years of the International Study Centre were a great success with a magnificent concert that will be much remembered. You must feel justly proud of realising your vision.

I look forward to welcoming you both to the Science Centre when you next visit.

Yours sincerely,

Stephen Pizzey

Stephen Pizzey

e-mail s.pizzey@science-projects.org
tel +44 (0)20 8741 2305
fax +44 (0)20 8741 2307

Subject: Signing of the Lieben Award contract
From: "Arnold Schmidt" <arnold.schmidt@tuwien.ac.at>
Date: Wed, 1 Oct 2003 09:45:54 +0200
To: "'Alfred Bader'" <baderfa@execpc.com>

Lieber Alfred,

danke für dein Fax. Ich freue mich sehr, dass jetzt alles unter Dach und Fach ist. Ich werde demnächst unseren Rektor treffen und ihm vom Lieben-Preis erzählen. Ich bin sicher, dass er meine Nominierung als Vertreter der TU-Wien veranlassen wird.

Herzliche Grüße,
Arnold

Subject: **news from Sherks**
Date: Sun, 14 May 2000 18:36:39 +0200
From: "Sherk Chemicals s.a.s." <sherk.chemicals@dada.it>
To: baderfa@execpc.com

Dear Alfred,

We understand that Helene and Jan Middledorf have been in touch with you and updated you with the news concerning Gloria Middledorf. Very briefly, in February Helene spent more than a week here in Florence and together with Anna got her placed in a rehabilitation center where they tell us she has reblossomed to the point of getting up and walking again, whereas everybody had been shaking their heads up till then in general consensus that such a feat was virtually impossible. Anna has consented to become Gloria's guardian, and together with Avv. Faraoni, a Florentine English-speaking lawyer whom we have known and respected for many years, as well as with other people we introduced Helene to, the way is being prepared to get the Middledorf situation finally in order by getting all necessary documents together so that Jan and Helene can do all that is necessary to set things right and see that Gloria and her property are finally well taken care of.

Anna and I did visit Maybridge in Tintagel, and once again I have to admit that you were right. They don't have any money. So you will be pleased to learn that as promised I did not give away the store. We are taking your very much appreciated advice and will be selling our compounds ourselves. We are going to place an ad, something we have never done before, in the Journal for Biomolecular Screening in August and will be renting a booth at the Society for Biomolecular Screening 2000 Conference in Vancouver this September, another first for us.

Concerning the Viagra case, as I told you in my letter of December 23rd, Pfizer offered to show us some documents that they claim would show that I have no case at all. Governor Cuomo told them fine, let's see them, and they replied that we would have to sign a Confidential Disclosure Agreement. They sent the draft and it became apparent that part of that Agreement was to be that Pfizer would not only not let ME see these documents (which apparently sometimes happens when the plaintiff is a "competitor" or someone who could use the highly classified information they say they would be exposing to view) but they would also not let Prof. Meth-Cohn see them either. They want us to choose a patent attorney to review these documents, and when asked why they said that it was because attorneys can lose their licence to practice if they say something false. Pfizer certainly has a wonderful opinion of chemists! So now we are discussing what our next step will be.
For Christmas Governor Cuomo sent us his latest book and first children's book, whose theme is based on what his father taught him when he was a boy: "You work and you wait. You never give up." That is exactly what we are doing.

Otto Meth-Cohn and his wife Jean spent most of last week as our guests here in Impruneta and we have had a chance to become great friends. Among many other interests they are avid hikers and yesterday we saw them off on a train up into the Appenines where they have a ten-day trek around the mountains planned out. They are the most wonderful people and I just know that you and Isabel will enjoy meeting them very much, and hope that will happen very soon.

Very best regards.

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
U S A

December 13, 2000

Dear Dr. Bader:

Vice-rector Schmidt and I (J.J) met with Professor Zahradník who promised to write to you soon.

And we are really glad that our season greetings can be accompanied by important good news.

After years of concentrated and unrelenting efforts, Masaryk University succeeded in gaining things necessary to begin, in the year 2001, construction of a new campus. MU now owns some fifty acres of land in Bohunice at the south-west edge of the city (where the high-rise hospital building dominates the skyline seen when coming on the divided highway from Prague), has full support of the city of Brno, and with the Czech Government backing, the necessary bank financing. MU Medical Faculty will be located there together with the Chemistry and Biology Departments of the Faculty of Science.

For chemists here, a new era is about to begin.

With best regards and all the best wishes for 2001 we remain

Sincerely Yours,

Jaroslav Jonas L. Skurský

Jaroslav Jonas *Ladislav Skurský*

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709
E-mail: baderfa@execpc.com

A Chemist Helping Chemists

August 14, 2000

Dr. Peter Schuster
Oberneuberg 78
A-8225 Pöllauberg bei Hartberg
Steiermark
AUSTRIA

Dear Dr. Schuster,

Isabel and I have just returned from Europe and so it has taken me so long to send you the material promised during our meeting in Vienna. You will have realized how very much I enjoyed that meeting.

Professor William Reynolds has really been terribly slow in working on his paper which he plans to submit to the *Journal of Chemical Education*, but the rough, early draft enclosed will give you some idea about his interesting thinking.

Also as promised, enclosed is a copy of the speech I gave when presented with an Honorary Doctorate in Brno.

Looking for my copies of Wotiz' book, of which I had bought 10 copies to share with friends, I note that I have just one left here, but now remember that I have another one left in England. I will mail that to you from England when we come there again, in November. Better late than never.

With all good wishes I remain

Yours sincerely,

Alfred Bader
www.alfredbader.com
AB/az
Enc.

Familie
Dr. Peter Schuster & Dr. Lily Wilmes,
Arthur & Oliver & Raphael

Oberneuberg 78
A-8225 Pöllauberg

Tel.: 03335 / 4849
Fax: 03335 / 4851

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709
E-mail: baderfa@execpc.com

A Chemist Helping Chemists

December 29, 1999

Dr. Peter Schuster
Oberneuberg 78
A-8225 Pöllauberg bei Hartberg
Steiermark
AUSTRIA

Dear Dr. Schuster,

What a pity that we could not meet in Ireland last August.

But Isabel and I plan to be in Vienna in June and perhaps we could arrange before two or three days in Styria, specifically, in a little place called Neuberg am der Mürz, where my grandfather took my mother in the 1880's and my mother took me between 1928 and 1934. It is a lovely place, probably not very far from you.

Isabel has been going through our old photographs recently and there found quite a few of you saying goodbye to us in Vienna. A few of these are enclosed.

I presume that you saw the Loschmidt book review in the August 2 Angewandte Chemie.

With all good wishes for a happy New Millennium I remain

Yours sincerely,

Alfred Bader
AB/az
Enc. - photos

Subject: **Re: three questions**
Date: Fri, 04 Feb 2000 14:53:50 -0800
From: "Sherk Chemicals s.a.s." <sherk.chemicals@dada.it>
To: baderfa@execpc.com

Dear Alfred,

Thanks for all this very interesting information.

On another front, I am forwarding to you for your information a letter that Anna just received from Jan Middeldorf's wife Helene. She will be coming to Florence towards the end of February and we will be assisting her in any way we can.

Tomorrow Anna and I are off to England, where on Tuesday we will be meeting with the Maybridge people.

John

At 03:16 PM 02/03/2000 -0600, you wrote:

> *Dear John,*
>
> *In response to your e-mail of today, I have never worked with Dr. Nick Kerton. I asked Dr. Christopher Hewitt, who worked closely with him in Gillingham, what he thought of Kerton. Chris told me that he is able, charismatic, political, and generally fair.*
>
> *I have not met Roger Newton.*
>
> *Roden (not Roland) Bridgwater worked for Aldrich close to 40 years ago. I met him when he had a small laboratory in Sussex and I then persuaded him to come to work at Aldrich. He is a very good chemist, immensely materialistic, and somewhat to the left of Lenin. He was terribly upset during the Cuban crisis about the way the US was treating Cuba. I didn't think that totally fair either, but it's not a totally black or white matter. Roden bought a very expensive house near where I live and as the housing market was rising rapidly, was able to sell it very profitably when he left Aldrich and returned to England. There, at one time, he actually ran for Parliament as an independent far left Socialist in opposition to the regular Labor party and received only a few votes. As I said, he was a good and hard-working chemist helped a great deal by a very humane and able wife. When last I visited him in Tintagel in Cornwall, he lived in a palace-like home. He wanted to sell his company for many years but would have liked to receive payment in Lichtenstein.*
>
> *Thank you for your two promises. I am relieved.*
>
> *With best wishes I remain*
>
> *Yours sincerely,*
> *Alfred Bader*
>
> *"Sherk Chemicals s.a.s." wrote:*
>
>> *Dear Alfred,*
>>
>> *I have just learned that the new managing director of Maybridge is a certain Dr. Nick Kerton who previously worked for Aldrich/UK.*
>> *Do you know him?*

\>>
\>> The CEO of Maybridge is Dr. Roger Newton, former director of
\>> chemical research at Glaxo Wellcome and presently also Resident
\>> Medicinal Chemist at the University of Cambridge. Perhaps you know him?
\>>
\>> Finally, is it true that Dr. Roland Bridgwater worked for Aldrich
\>> before setting up Maybridge?
\>>
\>> Very best regards.
\>>
\>> John
\>>
\>> PS I promise not to give away the store, and I will make certain
\>> that any payments are guaranteed. Thank you for this advice.
\>>
\>> Dr. John Sherk
\>> Sherk Chemicals sas
\>> Viale Galileo int. 26B
\>> 50125 Florence, Italy
\>> Tel: +39055207040
\>> E-mail: sherk.chemicals@dada.it
\>
\>
\>

Sussex

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

Subject: **Rare chemicals**
Date: Wed, 19 Jan 2000 09:42:33 -0500 (EST)
From: "Ian D. Spenser" <spenser@mcmail.cis.McMaster.CA>
To: baderfa@execpc.com

Dear Alfred   January 19, 2000

Thank you very much for your fax message which I received this morning.

I will await a communication from Bob Wendler. Again many thanks for your good offices.

Sincerely   Ian

Ian D. Spenser   Professor Emeritus

Department of Chemistry
McMaster University
Hamilton, Ont., Canada
L8S 4M1

Tel: (905) 525-9140; x23245
FAX: (905) 522-2509

spenser@mcmaster.ca

fax 298 7958

3 pages

Bob.
Please handle.
The 200 compounds
are bound to be
interesting.

To Bob Wandler

McMASTER UNIVERSITY
Department of Chemistry
1280 Main Street West, Hamilton, Ontario L8S 4M1
Telephone: (905) 525-9140
FAXMAIL (905) 522-2509

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202

Dear Alfred,

January 11, 2000

As soon as I heard from you last November 1, I prepared about 200 samples for transfer to the Bader Library of Rare Compounds.

I assumed that I would have a letter from Bob Wandler with instructions. In particular I thought he would tell me who at Sigma-Aldrich in Oakville would take over the samples on Wendler's behalf and arrange shipment to Milwaukee.

Two months later I have not yet heard from Bob Wendler and the samples are still sitting here. I presume that this delay is due to hold up during the holiday season. I am going off on a three week vacation to the Caribbean in the middle of February, and would very much like to complete the transfer of the samples before then. I wonder whether you would be willing to help getting things on track.

With best wishes for the New Year (since I am a purist it is my view that the new century and the new millennium start on January 1, 2001) and my best regards,

Yours sincerely

Ian

Ian D. Spenser
Professor Emeritus

FAX FROM:

Dr. Alfred Bader
924 East Juneau Avenue
Astor Hotel -Suite 622
Milwaukee, WI 53202
Ph: (414) 277-0730
Fax: (414) 277-0709
e-mail: baderfa@execpc.com

A Chemist Helping Chemists

January 18, 2000

TO: Professor Ian Spenser
McMaster University

Page 1 of 1

FAX #: 905 522-2509

Dear Ian,

In response to your letter of January 11th received only today, I am responding immediately by fax simply because I do not trust our mails.

Perhaps Bob Wandler is greatly overworked and just now he is traveling for a few days so I have been unable to telephone him. Or perhaps Bob's request to our Canadian operation just fell between chairs there.

In any case, I am sending Bob a copy of this fax and of your letter, asking him to phone or fax you to arrange for the transfer.

With all good wishes I remain

Yours sincerely,

Alfred Bader
AB/az
C: Bob Wandler (home)

November 1, 1999

Ian D. Spenser, Professor Emeritus
McMaster University
Department of Chemistry
1280 Main Street West
Hamilton, Ontario L8S 4M1
CANADA

Dear Ian,

In response to your letter of October 22, Isabel and I have no plans to come to Canada until the opening of the Isabel Bader Theatre in Toronto and of the new Art Museum at Queen's University. The latter will be in May and the theatre probably later.

But the idea of getting your samples to Sigma-Aldrich near Toronto is a very good one. I am sending a copy of your letter and of my reply to Bob Wandler, the man in charge of the Library, and I am asking him to be in touch with you, to coordinate the shipment.

Bob is able and fair and would, I am confident, arrange for prompt payment.

Isabel and I are leaving for England and Holland on November 4th and will not return home until December 20th, but I will try to be in touch with Bob before we leave to discuss all this.

With all good wishes, particularly for the new Millennium, I remain

Yours sincerely,

Alfred Bader
AB/az
C: Bob Wandler

Dr. Ladiskav SKURSKÝ

~~Departement of Biochemistry~~
~~Faculty of Science~~
~~Masaryk University~~
~~Kotlářská 2, 611 37 Brno~~
~~Tel.: 05/41129347~~
Fax: 05/41211214

Private:
Zborovská 1a
616 00 Brno
Tel.: 49254076
Skursky@brn.pvt.cz

Brno, Dec 10, 2001

Dear Dr Bader,

The first year of the new century is approaching the end and people start thinking about their „Season's Greetings"

Since I have been accepted among your friends I assume that you will again find the necessary patience to read a longer letter from me

First, I wish to express my best „Season's Greetings" to both Dr Isabel and you, and wish to both of you as a complete fulfillment of your personal wishes as possible. I confess, that here, among those who had the honour and pleasure to get into contact with both of you, the habit prevails to speak about „The Baders". I hope you would not find it excessively familiar (or unpolite).

On this occasion and in this mood, I cannot resist the temptation to load your patience with a sort of "personal report on what, I believe, is not indifferent to you

It is needless to say that since your last visit at Masaryk University, there is a feeling (both in the Institution and in a group of individuals) of a sort of close relationship with you. Its main aspect is <u>responsibility</u> for the burden you have put on us. It is very challenging.

My colleagues organic chemists have not succeeded yet in selecting the proper person for the Loschmidt chair. However, I am sure, they will finalize the search soon.

I also think that you will be pleased to learn

— over -

that the bearer of your recent special stipend, Dr. Peter Klan, will soon be promoted (in a process called here „habilitation") to the position of Associate Professor. He is doing very well in the field photochemistry. Also it might be worthwhile mentioning, that he is presenting his basic course on photochemistry in English. (He follows the attitude of his tutor, Prof. Jonas.) I have to say with pleasure (and with some pride too) that English is increasingly familiar to our chemistry students.

— To be honest I have to say that this applies even more for the students of physics. — This sparkles an association in me which I wish to share with you since it is not free of a relation to your activities. In 1995, there were three friends of mine, physicists, also participating at the „Loschmidt Symposium." (Everybody knows that it was you, Dr Bader, who was the principal – if not the only one – initiated and supporter of this undertaking of the Vienna University.)

The physicists paied in Vienna, of course, their main attention to the Loschmidt's physical studies, although the rediscovery of the treasure which had been hidden more than a century was a revelation for them also.

The Symposium proceedings exist here in three exemplars and they have been utilized for an intense seminar activity. For most physicists the Czech roots of Loschmidt was a big surprize, altthough - even before the Symposium - they knew much more (than e.g. me) on the physical achievements of L. I myself was only aware of his L. number.

Recently I was able to learn more on efforts which our „Institute of theoretical physics and astrophysics" headed by a young Professor Michal Lenc. (The name is, obviously, a charming Czech assimilation of the german LENZ.

I am amazed and pleased, how especially two young members of the Institute are contributing to studies, on a contemporary level, of course, of physical problems which could be traced back to L.

I confess envying them that they were able to attract (as internal members!) one young Swede and one young Austrian.

Just to let you taste a little gossip, I am revealing, that in one of those two new aquisitions, the heart of a young lady (now wife of one of those men) was a factor. — See, how important women might be for raising the progress of science!

I am mentioning all this as an enviable contrast to the (so, far) unsuccessful effort of

- cont. -

Potáčka et al. to fill the L. Chair.

If I may still keep this gay tone for a while, I would jokingly speculate that the physicists might be afraid that your accomplishments in Loschmidt's case could virtually somehow overshadow the L.'s importance for physics. – And this could stimulate their own efforts… .. might „jalousness" be a driving power?

But back to seriousness. – Before I conclude this voluminous (but, sorry, somewhat diluted) report I wish to mention just briefly, that the „fight" for L.'s commemorative stamp and also the efforts to set up a plate on the wall of the monastery school at Ostrov (Schlackendorf) have still been in their processes. I am convinced that, at the end, both the Baders and we will finally see the success.

At the end I dare to report preliminarily on my contacts with a television journalist (of a comparatively high rank) Mr Aleš Lowak. He is the chairman of the „Society of friends of Izrael" as well as chairman of the „Society of friends of the Moravian Gallery"; in this position he was aware of your sponsoring activities in favour of young art historians (like Mrs. Pelouśková-Worgötter). He, of course, knew nothing about chemistry or physics. I am almost a little proud that I succeeded to animate him for the (Kekulé)-Loschmidt-Bader Story. He now would like to compose a TV-film on the whole subject (within a series of programs designed to popularize science. I have accepted his suggestion to prepare for him a preliminary outline of the script. I hope to be able to do something on my own and, to find cooperators. The tentative titel would be „Chemistry and Rembrandt" or „A journey from Ch to R."

Concerning K. it will deal with both his faces (Ch.+Ph.). Mr Lowák also wishes to cover the aspects of scientific moral (Kekulé's neglection of his predecessors). He also wishes to include more data on Kekulé's ancestors. You might know (from Wotiz) that the Czech high school teachers, explaining the benzene structure, almost regularly attach the legend on Kekulé's relation with a noble family expelled from Bohemia during the forcefull recatholization of Czechs after the religion-related wars in the 17th century.

Last but not least, Mr Lowák asked me to act as a mediator between the two societies and you. They would like to ask you for two lectures for them on the occasion of your next visit to Brno. I dared to express the hope that, probably, you would meet their demands. – But there is time enough, anyway. Soon (I hope) he will bring me a letter for you which I am supposed to translate (since he does not trust his language proficiency).

– over –

I am finishing with the hope to hear from you at a suitable time.

Best regards to both of you!

Yours very sincerely

L Skrinsky

P.S.

The ending year has been a very good one, mainly thanks to The Baders. But I feel I have to attach an appology. Due to very friendly attitude of The Baders towards me I was in a temptation to dare to invite you to our house at least for a cup of coffe and a chat. - Sorry that it did not come thru. A process was going on within the Skrinsky couple which was concluded finally by the recent divorce.

Forgive me.

FAX FROM: *Dr. Alfred Bader*
924 East Juneau Avenue
Astor Hotel -Suite 622
Milwaukee, WI 53202
Ph: (414) 277-0730
Fax: (414) 277-0709
e-mail: baderfa@execpc.com

A Chemist Helping Chemists

May 1, 2000

TO: Dr. Brady Clark
Sussex Research Lab

Page 1 of 2

FAX #: 613-954-5242

Dear Dr. Clark,

I am so happy to have your fax of April 28th, telling me that your partner has finally agreed to sell his shares in your very good company.

If perchance you plan to visit Aldrich in Milwaukee, try to schedule your visit for a time that I am here. I'd love to have an hour or two to chat with us. But please remember that I travel a good deal.

From this coming Thursday until next Tuesday I will be in Kingston and Toronto and the weekend following in Cleveland. Then from May 30th to July 28th I will be in Britain and on the continent.

What I would like to talk to you about is your efforts with two companies, Sussex Research and TheraDigm. I fear that you may be making a mistake splitting yourself in two that way and that along the line you will have all sorts of conflicts of interest. Why not make both efforts through the already well-established company, Sussex Research?

Isabel's book was published as a very limited edition by the University of Toronto Press with the ISBN #0-7727-5700-3. I do not

know whether Ottawa bookstores will carry the book, but they could probably still get you a copy from the University of Toronto Press.

With all good wishes I remain

Yours sincerely,

Alfred Bader
AB/az

Sussex

[illegible]

ISBN
0-7727-5700-3

E-mail: brady.clark@nrc.ca
URL: www.sao.nrc.ca/~sussex

100 Sussex Drive, Ottawa
Ontario, Canada K1A 0R6

Fax: (613) 954-524

[illegible]
[illegible] 17
[illegible]
[illegible] Republic

[illegible] 3 [illegible]

Dear [illegible]

[illegible] content [illegible] at the Trinity [illegible]

[illegible]

There [illegible] from me.

But I [illegible] comment [illegible] establishing [illegible]

It [illegible] an exaggerated [illegible] enormous [illegible] amount [illegible]

[illegible]

[illegible] family members [illegible]

[illegible]

[illegible]

Thank you for your patience [illegible]

Best wishes [illegible]

Sincerely yours

[illegible]

FAX FROM:

Dr. Alfred Bader
924 East Juneau Avenue
Astor Hotel - Suite 622
Milwaukee, WI 53202
Ph: (414) 277-0730
Fax: (414) 277-0709
www.alfredbader.com
e-mail: baderfa@execpc.com

A Chemist Helping Chemists

September 30, 2003

TO: Professor Arnold Schmidt Page 1 of _1_

FAX #: 011 43 1588 01 38799

Dear Arnold,

I am happy to be able to tell you that the Lieben Award contract has been signed and the money transferred to the Joint, and so the first $54,000 should be in the bank account of the Academy within a couple of weeks.

Of course I very much hope that you will be the TU representative and Christian Noe the representative of the University.

With many thanks for all your help and with best wishes I remain

Yours sincerely, Herzliche Grüsse

Alfred Bader
AB/az

TRANSMISSION VERIFICATION REPORT

TIME : 10/01/2003 12:55

DATE,TIME	10/01 12:54
FAX NO./NAME	0114315880136739
DURATION	00:00:26
PAGE(S)	01
RESULT	OK
MODE	STANDARD ECM

THE
SCRIPPS
RESEARCH
INSTITUTE

Prof. Peter G. Schultz
Department of Chemistry
10550 North Torrey Pines Road
La Jolla, California 92037

tel 858 784 9300
fax 858 784 9440
e-mail: schultz@scripps.edu

April 23, 2001

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202

Dear Alfred,

I did receive the autobiography -fascinating. Thanks again and best regards.

Sincerely yours,

Peter G. Schultz
Professor, Department of Chemistry
The Scripps Research Institute
and
Director, Genomics Institute of the
Novartis Research Foundation

PGS/ca

Dear Gideon,

Thank you for your e-mail of April 21.

I am happy to know that EraGen is doing well. I limit myself in all my investments where I do not really know the company well, and I would not like to acquire more of EraGen's stock. Thank you for giving me the opportunity.

Best wishes,
Alfred Bader

Gideon Shapiro wrote:

> Dear Alfred,
>
> Thank you for your consideration. I understand perfectly your choice not to invest in Somatocor directly since it is very risky at the very start. EraGen is now well on its way with customers for both product lines. I intend to take the money that I have put into EraGen and use it as the starting capital for Somatocor.
>
> EraGen's lawyers tell me I can sell a small fraction of stock that I have in EraGen to do this. To this end if you are interested in purchasing up to $50,000 worth of stock at the last $1.50 per share price before the company completes the next round of financing at ca.$3.00 per share please let me know in a reply to this e-mail at your convenience.
>
> Once again thank you for your support of Steve and I in EraGen and best regards.
>
> Gideon
>
> >From: Bader Fine Arts <baderfa@execpc.com>
> >To: gideon_shapiro@hotmail.com
> >Subject: Somatocor
> >Date: Fri, 20 Apr 2001 10:11:01 -0500
> >
> >Dear Gideon,
> >
> >I am happy to see from your e-mails that you are continuing to work with
> >EraGen and hope that that company will succeed.
> >
> >
> >My investment in EraGen was sort of on the borderline of what I have set
> >for my investments. I have known Steven Benner and admired him for a
> >long time and the combination of the two of you working together
> >persuaded me to invest.

\>
\>Of course it seems to me that Somatocor has a good chance to succeed,
\>but its work is clearly way beyond my own knowledge.
\>
\>I do hope that you will understand why I will not invest in Somatocor.
\>
\>With all good wishes I remain
\>
\>Yours sincerely,
\>Alfred Bader

Subject: **Somatocor**
Date: 9 Apr 2001 17:09:11 -0700
From: gshapiro@somatocor.com
To: baderfa@execpc.com

Dear Alfred,

I have mailed you a package of information today that you should receive by the end of the week.

Included with the cover letter are the following documents:

1. An Executive Summary
2. An Overhead Presentation format Summary
3. Lecture Review on Carcinoid and Sandostatin
4. Letter from specialist clinician E. Woltering

I am getting very excited about the impact that the first orally and the first centrally active somatostatinergic drugs will have on

Best regards,

Gideon

Post-it® Fax Note R7673
Date 3/16
# of pages 2
To PROF MG FINN
Fax# 858 784 8850
From ALFRED BADER
Phone# 414-277-0730

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709
E-mail: baderfa@execpc.com

A Chemist Helping Chemists

March 16, 2001

Professor M. G. Finn
Scripps Research Institute
The Skaggs Institute
10550 North Torrey Pines Road
La Jolla, CA 92037

Dear Professor Finn,

Thank you for your letter of March 7th.

My wife and I look forward to arriving in San Diego on Friday, March 30th, and we will be staying at the Wyndham Emerald Plaza.

We will not be able to attend the Sharpless' brunch on Saturday morning but hope to be at the open house in the afternoon. I would appreciate directions on how to get from the hotel to the open house.

On Saturday evening we will be at a Project SEED dinner arranged by the ACS, and so we will not be able to be at your dinner.

On Tuesday evening we have to be at the formal ACS dinner, presenting the Bader Award in Biochemistry.

Of course I much look forward to chairing the meeting on Wednesday afternoon.

We are now registered for the group reunion.

I look forward to meeting you and many friends on Saturday afternoon.

With best regards I remain

Yours sincerely,

Alfred Bader
AB/az

Dear Mr. Stevens,

S&S Chemical is a remarkable company and I want to congratulate you on what you have accomplished.

It reminded me of the position of Aldrich in the 1950s and 60s when our only major competitor was Eastman-Kodak, which really did not care very much for that part of the business. Baker Petrolite clearly does not care very much either and is turning away potential customers. Eastman-Kodak no longer is in this business but of course I never considered approaching Eastman to buy their fine chemicals business, but perhaps you might consider purchasing Petrolite's business.

Now, two important questions:

1. Why are you working with VECO, beginning in January 2003 up until now. Wouldn't your time be spent much better working for S&S?

2. The key question is how well you really get along with Richard Nelson and how competent is he? If really competent and you can trust him completely, then his projected income is too low.

To turn now to your income statement, you showed a loss in 2003 of $16,000 and income in 2004 of $112,000. Your income in 2005 will be very much higher and hence you should not consider selling part of your business to others until you can show the very positive improvement for 2005.

Your year end inventory of $309,000 appears to have increased considerably higher than your sales. I assume that there is a very good reason for this.

My recommendation to you is not to consider going public or selling part to others until your sales and earnings have increased as you project for the next several years.

I personally have invested in a number of small companies, usually through a company called Bader & Bernstein, which is owned 50% by myself and 50% by a very good friend and able attorney, Mr. Joseph Bernstein. At some point please allow me to share what you sent me with him.

With best personal regards and again, heartiest congratulations, I remain

Yours sincerely,
Alfred Bader

bruce stevens wrote:

> S&S CHEMICAL CONFIDENTIAL – LIMITED ACCESS
>
> Dear Sir:
>
> Thank you very much for going to the trouble to fax me your letter on confidentiality. I greatly appreciate it and hope I did offend you by sending the original Confidentiality Agreement.
>
> Please find the attached Business Summary. I would greatly appreciate the opportunity to discuss it with you at your leisure.
>
> I also look forward to receiving your autobiography.
>
> Sincerely,
>
> Bruce Stevens
> S&S Chemical, Inc.
> PO Box 2027
> Durango, Colorado 81302
>
> (970) 749-5304 phone
> (970) 375-2816 fax
>
> ---
>
> This message scanned for viruses by CoreComm
>
> --
> No virus found in this outgoing message.
> Checked by AVG Anti-Virus.
> Version: 7.0.308 / Virus Database: 266.8.1 - Release Date: 3/23/2005

Dear Mr. Stevens,

Thank you for sending me your confidential report which I will study this coming weekend. I will then share my thinking with you next week.

I am sending you my autobiography by mail today.

With best regards I am

Yours sincerely,
Alfred Bader

S&S CHEMICAL CONFIDENTIAL - LIMITED ACCESS

BUSINESS SUMMARY

S&S CHEMICAL, INC.

P.O. Box 2027
Durango, Colorado 81302-2027
(970) 749-5304

Prepared by:
Bruce N. Stevens, General Manager
January, 2005

Table of Contents

List of Appendices

Executive Summary

S&S Chemical, Inc. has been engaged in the manufacturing of various wax products, primarily POLYBOOST™ polymers, for greater than five years. At the request of several of our customers, S&S commercialized a new line of synthetic waxes, PRECISIONMelt™ polyethylenes, in 2004. As with the POLYBOOST polymers our only competitor for this new product line is Baker Petrolite.

In addition to commercializing a major new product line in 2004, S&S Chemical continued to grow sales of POLYBOOST polymers at the phenomenal rate of 90%. This remarkable growth was achieved by expanding sales at existing customers by greater than 70% as well as increasing our customer base by 110%. A two year contract was signed with one of these new customers, Owens Corning, that will make them our largest customer by generating 52% of 2004 revenue in 2005. Our largest customer, Alphamin, also placed an order for 260 tons of POLYBOOST 165 to be delivery monthly until September, 2005. These two contracts alone represent greater than 104% of all of our 2004 revenue.

2004 Earnings growth, although limited due to investment in the development of the PRECISIONMelt polyethylenes, was still a staggering 52%. Earnings growth in future years is expected to be significantly higher due to:

- continued sales growth of POLYBOOST polymers,
- penetration of the significantly larger PRECISIONMelt polyethylenes market,
- realizing higher gross profit margin of the PRECISIONMelt polyethylenes,
- commercialization of additional customer requested products.

S&S Chemical has recently been approached by several companies interested in taking equity positions in our company. The purpose of this Business Summary is to introduce S&S Chemical to these companies and others like them. Initially our products are introduced following by a description of our business and the industries we serve. Next, our sole competitor is discussed. Finally, the historic and proforma financials are presented in detail.

Products

Existing Products

POLYBOOST™ polymers

POLYBOOST polymers were introduced by S&S Chemical in 2000 as direct, drop-in replacements for Vybar polymers, which were developed and patented by Petrolite Corporation in the late 70's. Vybar polymers are currently offered to the market on a limited basis, exclusively by Baker Petrolite. Baker Petrolite was formed in 1998 when Baker Hughes purchased Petrolite Corporation. POLYBOOST polymers are high molecular weight, non-linear polymers. They are waxes - plastic solids at room temperature.

New Products

PRECISIONMelt™ polyethylenes

PRECISIONMelt polyethylenes are direct, drop-in replacements for Polywax polyethylenes that are currently offered to the market on a limited basis, exclusively by Baker Petrolite. PRECISIONMelt polyethylenes are linear, low molecular weight polyethylenes that are produced by polymerizing ethylene in a very precise manner. They are basically synthetic waxes that melt over a 1°F temperature range rather than over the typical 3-5°F temperature range of crude oil derived waxes.

HICHAIN™ Alcohols

HICHAIN alcohols are direct, drop-in replacements for Unilin alcohols that are currently offered to the market on a limited basis, exclusively by Baker Petrolite. HICHAIN alcohols are long chain primary alcohols. HICHAIN alcohols are waxes with alcohol functionality.

The primary uses of all of these products will be discussed in detail in the Industry section of this Business Summary.

Corporate History

The operation of S&S Chemical began in January 1999 with the search for a contract manufacturer to produce POLYBOOST polymers. POLYBOOST 165 polymer was successfully commercialized in November, 2000. After several months of consistent growth, sales of POLYBOOST 165 began skyrocketing in the summer of 2002 when an initial 40 foot container load of product was shipped to Sasol in Hamburg, Germany. Sasol is the world's largest wax compounder. This growth was expanded when a Supply/Distribution Agreement was signed with Alphamin in August, 2002 to distribute S&S Chemical products in Europe.

Efforts to diversify S&S Chemical's product offerings also began in the summer of 2002 with the commercialization of POLYBOOST 130. POLYBOOST 130 is a lower melting version of POLYBOOST 165 and is used primarily in the manufacturing of container candles. Diversification efforts continued when several existing customers began requesting samples of additional products from S&S Chemical in 2002. These additional products include PRECISIONMelt polyethylenes and HICHAIN alcohols. PRECISIONMelt 451 polyethylene was commercialized in November, 2003. This is the lowest melting point, nominally 160 °F, version of a line of 5 synthetic waxes with various melting points. Sales of PRECISIONMelt 451 into the Toner industry began in December, 2003 through Honeywell.

PRECISIONMelt 507 and 661 polyethylenes were successfully commercialized in August, 2004. These products have nominal melting points of 180 °F and 200 °F, respectively. Sales of PRECISIONMelt 661 into the Thermoset Industry began in September, 2004 through Honeywell. Sales of PRECISIONMelt 507 into the Personal Care and Cosmetics industry began in September, 2004 through Jeen International.

Plans to commercialize PRECISIONMelt 998 and 2000 polyethylenes and HICHAIN 425 alcohols within the next few months are currently in place. Several other products including direct, drop in replacements for Polymekon and oxidized waxes produced by Baker Petrolite have also been requested by various customers and direct, drop-in replacements are under development.

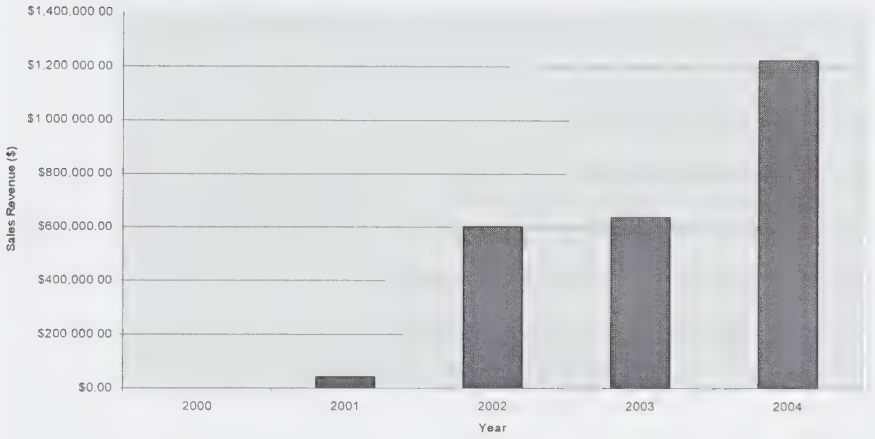
Bruce Stevens was the sole employee of S&S Chemical until March, 2004. Mr. Stevens worked for Petrolite Polymers Division between 1989 and 1996 in various capacities including Technical Manager, Production Manager, and Strategic Projects Manager (which entailed managed the Division's Business Planning and Mergers & Acquisitions). During his tenure at Petrolite, Mr. Stevens manufactured numerous commercial batches of Vybar polymers, Polywax polyethylenes, and Unilin alcohols. He also developed multiple experimental products based on the Vybar, Polywax, and Unilin technologies. Mr. Stevens left Petrolite Polymers Division just prior to the company's acquisition by Baker Hughes Corporation in early 1997. Mr. Stevens' resume is attached as Appendix 1.

Current Year Results

Once again, sales of POLYBOOST polymers have increased dramatically during 2004. In fact, 2004 sales exceeded 2003 sales by greater than 90% as shown below in Figure 1. This dramatic increase was due in large part to strong sales growth of over 70% at existing customers, as well as a 110% increase in our customer base.

S&S CHEMICAL LLC
Sales History

S&S CHEMICAL CONFIDENTIAL - LIMITED ACCESS



The acceptance of PRECISIONMelt polyethylenes has been so overwhelming that lucrative Supply/Distribution Agreements containing minimum Sales Quotas have been signed with Sasol Wax Americas, Jeen International, and RAND Trading for various markets. These customers are in addition to Honeywell who initially approached S&S about producing PRECISIONMelt 661. In fact, Honeywell has already purchased significant quantities of both PRECISIONMelt 451 and 661. Negotiations are also currently underway with at least 4 other premier, well established companies that have also approached S&S about distributing our products. All of these Supply/Distribution Agreements also include significant opportunities for POLYBOOST polymers.

2004 Earnings also set another record with a greater than 52% increase over 2003 Earnings. In addition to record sales, the settlement of the lawsuit with Chusei significantly increased 2004 Earnings. The lawsuit was the result of Chusei's negligence during the manufacturing of the initial batch of POLYBOOST polymers in 1999 and resulted in a $125,000 award to S&S. The settlement of this suit will also dramatically decrease S&S Chemical's on going legal expenses. The commercialization of PRECISIONMelt polyethylenes as well as the imminent commercialization of HICHAIN alcohols will also dramatically increase new product sales and eliminate the need for additional product development costs for these products further increasing earnings in 2005. Finally, the significantly higher gross profit achievable with the PRECISIONMelt and HICHAIN product lines will dramatically add to future earnings.

Another significant event that dramatically strengthened S&S during 2004 was the hiring of Rick Nelson as S&S Chemical's Vice President of Sales and Marketing. Mr. Nelson has greater than 18 years of experience marketing various waxes predominantly in the Candle Industry for several well respected companies. He also has extensive logistics expertise which has benefited S&S. The addition of Rick has also geographically expanded S&S' offices to include our Chicago Sales Office in Carol Stream, Illinois. Rick's resume is attached as Appendix 2.

One of Owens Corning's lead R&D Engineers contacted S&S Chemical in September, 2004. Christopher Hawkins said that his primary goal for 2004 was to find an alternative to BakerPetrolite's Vybar 260. As a result, he performed a search for "Vybar alternative" on Google.com and found S&S Chemical's website. After a short 10 weeks of evaluation by Owens Corning, S&S Chemical signed a 2 year contract to supply Owens Corning with at least 45,000 pounds of POLYBOOST 130 per month. This significant quantity will make Owens Corning at least our second largest customer with 2005 Sales of at least $630,000.

Owens Corning uses POLYBOOST 130 as a sizing agent in their fiberglass manufacturing process in Norway. They plan to add a third production line at this facility during late 2005 or early 2006 which will further increase their demand for POLYBOOST 130 by 50%. In addition, we have learned that lower viscosity batches of POLYBOOST 130 increase the tensile strength of the fiberglass. As a result, we are preparing samples of an improved POLYBOOST 130 with lower viscosities so we can tailor a new product to meet Owens Corning's specific needs.

Another significant event that occurred in 2004 was receiving a purchase order from Alphamin, our largest customer, for $645,000 of POLYBOOST 165. Shipments will occur through September, 2005. This order only represents Alphamin's base business and we have in fact already received an order for product that is in addition to this significant purchase order.

The combined value of just the contracts that are already in place for 2005 Sales with Owens Corning and Alphamin represent 104% of all of our 2004 revenue.

In addition to these 2004 events, a start-of-the-art computer network was purchased and installed in 2004 to facilitate the operation of S&S. All members of S&S can access this network remotely and S&S' valuable information is automatically backed up on a routine basis. Another significant event was the launching of our website in mid April. Our website has already led to the signing of a 2 year million dollar contract with Owens Corning. Finally, S&S joined the Quality Center for Business, a business incubator in Farmington, New Mexico in October, 2003.

Industries

POLYBOOST Polymers

Candle Industry

POLYBOOST polymers are used primarily to bind oil in paraffins. POLYBOOST polymers' ability to bind oil in paraffins fulfills Wax Compounders' needs for additives that allow them to formulate premium priced, specialty products. Wax Compounders sell these premium priced, specialty products to a wide variety of markets, primarily Candle Manufacturers. These formulations enable the Wax Compounders to differentiate themselves from their competitors.

POLYBOOST polymers are also sold directly to Candle Manufacturers to allow them to dramatically increase the amount of fragrances and colorants they can put in their candles without experiencing oil bleed problems. POLYBOOST polymers also disperse the fragrances and colorants more evenly throughout the candle reducing pooling of the fragrances and colorants. Evenly dispersed fragrances and colorants also reduce sooting which can be caused by pools of undispersed fragrance reaching the candle wick during burning. Some consumer groups have tried to tie sooting to potential health problems in recent years.

Fiberglas Industry

POLYBOOST polymers were also sold for the first time in 2004 into the Fiberglas Industry. POLYBOOST 130 is a very effective sizing aid in the Fiberglas Manufacturing process. In fact, lower viscosity batches of POLYBOOST 130 dramatically increase the tensile strength of the finished fiberglas.

Investment Casting Industry

POLYBOOST polymers were also sold into the Investment Casting Industry for the first time in 2004. POLYBOOST 165 is very useful in the Investment Casting Industry because they reduce the amount of shrinkage associated with a wax when it cools. This reduced shrinkage creates a mold that is closer to the actual size of the original piece that is being replicated.

PRECISIONMelt Polyethylenes

PRECISIONMelt Polyethylenes are synthetic waxes that melt over a precise 1°F temperature range rather than over the typical 3-5°F temperature range of crude oil derived waxes. This precise melting characteristic dramatically enhances the performance of a multitude of products that use waxes as additives that significantly enhance the performance of the product. PRECISIONMelt polyethylenes also represent the missing premium product offering that Polyethylene (PE) Wax Formulators, such as Sasol Wax Americas, have been pursuing for years. As a result of the lucrative Supply/Distribution agreements signed with S&S, these PE Wax Formulators are now

able to compete with a full range of products including premium PRECISIONMelt polyethylenes.

HICHAIN Alcohols

HICHAIN alcohols are long chain primary alcohols. They are waxes with alcohol functionality. They represent very attractive alternatives for alcohol purchasers needing long chain products as well as wax purchasers needing alcohol functionality. Alcohols are one of the key classes of chemicals using the Chemical Industry. Their major uses are as building blocks for production of other chemicals, disinfectants, and surfactants. One of the hindrances that prevent alcohols from being more widely used in a variety of applications is their adverse health effects. For example, low molecular weight alcohols such as methanol and ethanol are skin and eye irritants. As a result, it is difficult to use methanol or ethanol in lotions and shampoos even though they are good surfactants. However, as the molecular weight of the alcohol is increased their adverse effects are minimized. For example, mystrial alcohol is used as a surfactant in "No More Tears" Johnson's Baby Shampoo. HICHAIN alcohols have significantly higher molecular weight than mystrial alcohol and therefore are even milder.

Until Unilin alcohols were introduced by Petrolite, the highest molecular weight alcohols were oleyl alcohols. HICHAIN alcohols are direct, drop-in replacements for Unilin alcohols. HICHAIN 425 has a molecular weight (425) that is nearly twice that of oleyl alcohol. In addition, HICHAIN alcohols can be produced with molecular weights as high as 1000.

Major Customers

Honeywell

PRECISIONMelt 661 polyethylene was initially developed in response to our second largest POLYBOOST customer's (Honeywell) desire to discontinue doing business with Baker Petrolite. In addition, Honeywell has tried to get Baker Petrolite to tailor a slightly higher molecular weight product to specifically meet Honeywell's Thermoset wax needs. After satisfying Honeywell need for a direct, drop-in replacement for their Polywax 655 polyethylene, S&S is now working to further secure Honeywell's business by producing PRECISIONMelt 700 polyethylene to specifically meet their Thermoset wax needs. In addition, Honeywell has always tried to purchase other Polywax grades and Unilin alcohols from Petrolite. Petrolite views Honeywell as a competitor and therefore will not sell these products to them. S&S realizes the significant depth of Honeywell's applications knowledge and will continue to work with Honeywell to develop the full line of PRECISIONMelt polyethylenes and HICHAIN alcohols to meet Honeywell's needs.

Sasol Wax Americas

With over 100 years of dedication to the wax industry, Sasol Wax Americas is a world leader in the development and marketing of high quality wax products from a variety of sources. However, for decades Sasol Wax Americas has been frustrated by selling

products that compete with Polywax polyethylenes but do not perform as well as Polywax polyethylenes in many applications. Seeing the opportunity to better serve their existing customers and capture significant marketshare, Sasol Wax Americas was one of the initial companies to approach S&S requesting the rights to distribute PRECISIONMelt polyethylenes in several markets. S&S and Sasol Wax Americas entered into a very lucrative, transparent Supply/Distribution agreement on May 13, 2004. In return for maintaining minimum Sales Quotas of 400,000 pounds by 6/1/05, 750,000 pounds by 6/1/06, and 1,000,000 pounds by 6/1/07 Sasol Wax Americas gained the ability to enter the US, Canadian, and select Latin American Adhesives, Inks, Toners, Polishes, and Mold Release Markets with the premium linear polyethylene technology in addition to the other 3 polyethylene technologies they have represent for decades. Sasol Wax Americas will also represent S&S Chemical's POLYBOOST technology at several Candle Manufacturers that they have served for many years.

Jeen International

Jeen International is one of the leading suppliers of specialty chemicals to the Personal Care & Cosmetics Industry. Jeen International hired Chris Tarletsky as their Sales & Marketing Vice President in 2001. Chris had been hired by Petrolite Polymers Division in 1996 after a nationwide prepaid headhunter search for an individual to initiate and manage a Personal Care & Cosmetics Strategic Business Unit. Mr. Tarletsky and Mr. Stevens worked hand in hand while at Petrolite Polymers Division establishing New Phase Technologies, Petrolite's Personal Care & Cosmetics Strategic Business Unit. After introducing Polywax and Unilin to the Personal Care & Cosmetics industry and growing sales from $0.5MM to over $7MM in 3 years, Mr. Tarletsky left Baker Petrolite. Mr. Tarletsky now has an ownership position in Jeen International with lucrative incentives to bring new technologies to the corporation. Jeen International approached S&S requesting the exclusive rights to distribute PRECISIONMelt polyethylenes and HICHAIN alcohols to the Personal Care & Cosmetics industry. S&S and Jeen signed a lucrative, transparent Supply/Distribution agreement with attractive minimum Sales Quotas during June, 2004.

Caromex

Several other significant opportunities have been presented to S&S Chemical as a result of Baker Petrolite and Calumet Industries dissolving their wax joint venture named Bareco Products. Bareco Products was formed in 1996 as a joint venture between Petrolite Polymers Division and Pennzoil Products. When Pennzoil Products exited the manufacturing business, Calumet Industries purchased Pennzoil's manufacturing assets and took Pennzoil's place as Petrolite's partner in Bareco Products. Petrolite put their low margin, commodity microcrystalline wax business into Bareco Products. In January, 2004 Petrolite and Calumet dissolved Bareco Products mainly due to the fact that Baker Petrolite would not let Bareco Products represent any of their specialty products – Vybar, Polywax, Unilin, etc. While Baker Petrolite tried to hire all 15 of Bareco's employees only 2 hired on with Baker Petrolite.

Bareco Products' International Sales Manager, Jose Montes, founded Caromex, while Bareco Products' General Manager and Sales Manager formed Clarus Products. Both

companies approached S&S about distributing our products in March, 2004. Jose, particularly, has maintained a strong distribution network for many years. He not only managed all of Bareco's Distributors, his grandfather started a candle and wax trading company in Mexico City many years ago. Jose's father now operates the candle and wax trading company. Jose's cousin until recently was Bareco's and Baker Petrolite's Central American Distributor. As a result of the dissolution of Bareco Products, Baker Petrolite has gone to all of their previous Bareco Distributors, many of whom were also Baker Petrolite Distributors, and told them that Baker Petrolite will now serve the market directly and no longer needs the services of the Distributors. Since Jose set up this entire Distributor network, he is very eager to supply these Distributors with direct, drop-in replacements not only for Bareco's previous product line but also for Baker Petrolite's specialty products. In addition, Jose has knowledge of all of Bareco's previous formulations and the ability to improve these formulations with S&S' direct, drop-in replacements for Baker Petrolite's specialty products. In fact, Caromex sold their first 12 metric ton container of POLYBOOST 165 to Compai in El Salvador in early June, 2004. Negotiations on a transparent Sales/Distribution agreement containing lucrative minimum Sales Quotas with Caromex should be completed shortly.

Markets

Candle Industry

2004 POLYBOOST polymer sales into the Candle Industry increased greater than 80% over 2003 POLYBOOST sales into the Candle Industry. As mentioned above, Sasol Wax Americas and Jeen International have several Candle Manufacturers they consider to be house accounts. Now that Supply/Distribution agreements are in place with these companies they will aggressively pursue POLYBOOST sales at these house accounts to help satisfy the minimum Sales Quotas in the agreements. Several well-established Distributors have approached S&S Chemical about representing POLYBOOST polymer to less than pallet consumers, mainly in the Candle Industry.

Worldwide Candle Sales continue to increase more than 15% per year. While consumers are demanding higher quality candles, many candle manufacturers are being forced to purchase lower quality paraffin waxes from China to compete with inexpensive imported candles from China. In addition, the availability of high quality waxes are under continued pressure as refineries upgrade their lube oil processes with hydrotreating technology that greatly minimizes the production of waxes.

Thermostat Industry

Honeywell has specifically requested S&S Chemical produce PRECISIONMelt 661. They currently purchase a 45,000 pound truckload of Polywax 655 each month to produce a product that is sold to the Thermostat Industry. Their key customers in the Thermostat Industry are Standard Thompson, Wahler, Watts, and Fuji Bellows. Honeywell uses Polywax 655 for this application because of its sharp melting point. However, Polywax 655 has significant batch-to-batch variation and Honeywell receives very poor customer service from Baker Petrolite. In addition, Honeywell would prefer to

purchase a slightly higher molecular weight version of Polywax 655 but Baker Petrolite will not develop a new product for them. After satisfying Honeywell need for a direct, drop-in replacement for their Polywax 655 polyethylene, S&S is now working to further secure Honeywell's business by producing PRECISIONMelt 700 polyethylene to specifically meet their Thermoset wax needs.

Toner Industry

Honeywell has also been selling PRECISIONMelt 451 into the Toner Industry. Their primary customers in the Toner Industry are Sony, Immak, NuKote, and NCR. Honeywell has formulated new products for this industry using the PRECISIONMelt 451 and are also selling the PRECISIONMelt 451 directly to these customers. The PRECISIONMelt 451 gives these customers a wax base that will allow their toners to set at a lower temperature thus saving them significant amounts. PRECISIONMelt polyethylenes augment the microcrystalline and paraffin waxes that Honeywell has sold into the Toner Industry for many years.

Sasol Wax Americas has also participated in the Toner Industry for many years. However, until now Sasol Wax Americas has been limited to selling Fischer Tropsch (FT) waxes and by-product polyethylene (PE) waxes into this industry. FT waxes are limited by their broader molecular weight distribution as well as their high end molecular weight tail that prevents them from being compatible with many toner formulations. By-product PE waxes are limited by their very broad molecular weight distribution and amount of branching. These limitations prevent by-product PE waxes from being compatible with many toner formulations. The PRECISIONMelt polyethylenes will allow Sasol Wax Americas to further serve their Toner customers with premiere technology that delivers significant formulating power.

Adhesives Industry

Sasol Wax Americas pioneered the introduction of waxes in the Adhesives Industry during the early 1950's when they signed an exclusive distributorship to bring FT waxes from Sasol in South Africa into North America. They also began supplying by-product PE waxes into this industry several years ago. However for the reasons mentioned above, FT and by-product PE waxes have limited applications in Adhesive formulations. Once again, the PRECISIONMelt polyethylenes will allow Sasol Wax Americas to further serve their Adhesives customers with premiere technology that significantly extends the formulation possibilities. Their major customers are HBFuller, Swift, and Hercules.

Intermediate Grinders/Blenders/Compounders Industry

Sasol Wax Americas has also been a significant player in the Intermediate Grinders/Blenders/Compounders market. These companies grind, blend, and compound various waxes, pigments, oils, and additives to make pastes that are sold into the Inks and Paints Industry. Once again the PRECISIONMelt polyethylenes will allow offer the Grinder/Blenders/Compounders with superior technology to improve the performance of their Ink and Paint compounds. Sasol Wax Americas' primary customers in the

Grinders/Blenders/Compounders Industry are Shamrock, Micropowders, Lawter, and Carroll Scientific.

Mold Release Industry

Another one of Sasol Wax Americas' primary markets is the Mold Release Industry. A wide variety of waxes are used to allow various substances, mainly plastics such as polyurethane foam, polyethylene resin, and polycarbonate resin, to release from the molds that are used to form these substances into a useable form. Once again, the PRECISIONMelt polyethylenes will allow Sasol Wax Americas to offer a significantly wider range of melt points and heats of fusion to use when designing mold releases for various plastics. Sasol Wax Americas' primary customers in the Mold Release Industry are Chemtrend and Michelman. In fact, Chemtrend has been very impressed with recent PRECISIONMelt 451, 507, and 661 samples and plan to begin purchasing these products very soon.

Personal Care & Cosmetics Industry

Many waxes are used in a wide variety of applications in the Personal Care & Cosmetics Industry. These various applications include lipstick base, eye shadow, foundation, fingernail polish, shampoos, toothpastes, and a wide variety of lotions to mention just a few. As mentioned above, Chris Tarletsky who now has an ownership position in new products he brings to Jeen International put all of Baker Petrolite's Polywax and Unilin Personal Care & Cosmetics business in place several years ago. Jeen has purchased both PRECISIONMelt 451 and 507 for market development sales at several of their existing customers.

Competition

The only competitor for POLYBOOST polymers, PRECISIONMelt polyethylenes and HICHAIN alcohols are Vybar polymers, Polywax polyethylenes and Unilin alcohols, respectively. These products are all sold by Baker Petrolite on a limited basis to select customers. Potential customers welcome the introduction of competition to Petrolite's previous monopoly in the sale of Vybar polymers, Polywax polyethylenes and Unilin alcohols for several reasons.

In 1996 Petrolite redirected their marketing strategy from being a performance additive supplier to providing value to their customers in specific key markets. This strategy caused them to limit the sale of products to only customers where the value provided to the customer was identifiable. However, most customers especially in formulation driven markets such as the Plastics and Personal Care Industries do not want their suppliers knowing their formulations much less how much value an additive lends to their formulation. As a result, most customers would rather not purchase their products from Baker Petrolite.

Another aspect of the fact that Baker Petrolite only sells their products to a limited portion of the market is that the ultimate market size for S&S Chemical's products is significantly larger than the portion of the market that Baker Petrolite chooses to serve. In fact, S&S Chemical has already sold our POLYBOOST polymers into portions of the market that have not been previously served by Baker Petrolite.

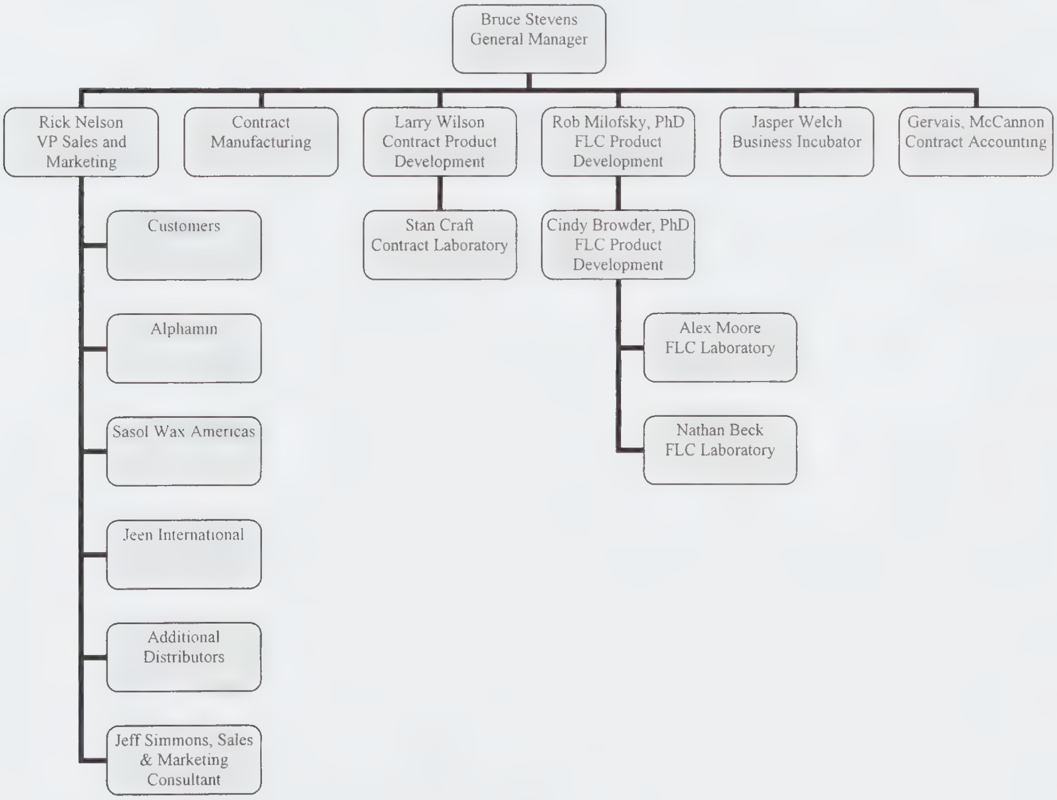
Baker Petrolite's customer satisfaction has also significantly deteriorated since they were acquired by Baker Hughes in July of 1997. In addition, the recent dissolution of Bareco Products discussed above under the Caromex paragraph has dramatically weakened Baker Petrolite's ability to compete in the marketplace.

Several factors also preclude additional competitors from entering the marketplace. The primary factor is that the majority of the middle market Specialty Chemical companies have been eliminated by acquisition. As a result, the relatively small niche markets that the POLYBOOST polymers, PRECISIONMelt polyethylenes, and HICHAIN alcohols serve are not large enough to gain the attention of large, multinational Specialty Chemical companies. In addition, the research that would have to be performed to develop the processes to make these products would be so large relative to the size of the markets that the return on the investment would not be large enough to justify the investment. S&S Chemical has a major advantage, since our development costs were relatively small since the technology was previously practiced by Mr. Stevens during his tenure at Petrolite.

Finally, the most important barrier to additional competition is that S&S Chemical has made significant improvements to the processes required to produce all three of our product families. Efforts are currently underway to patent these initial improvements as well as make further improvements to the technologies to extend the patents even further.

Organizational Structure

Increasing sales have allowed S&S Chemical's staff to grow during 2003 and 2004. As mentioned above, Rick Nelson was hired as our Vice President of Sales and Marketing in March 2004. In addition, S&S Chemical has contracted the services of Larry Wilson, President of LARAN Consulting, to assist in development of the PRECISIONMelt polyethylene and HICHAIN alcohol technology. We have also contracted the services of Stan Craft at Chempro to perform bench scale laboratory experiments to assist Larry Wilson in new product development. Jeff Simmons, President of X-selleration as well as Petrolite's previous International Sales and Marketing Manager, was also contracted during 2004 to assist in sales and marketing strategy development as well as website development. Finally, a second Fort Lewis College (FLC) student has been added to increase our new product development outside of the PRECISIONMelt polyethylene and HICHAIN alcohol area. In fact, both students worked on a full time basis during the summer of 2004. Finally, S&S began contracting Gervais, McCannon & Associates to perform our Accounting needs.



FINANCIAL PLAN

Balance Sheet

The 12/31/04 Balance Sheet, attached as Appendix 3, demonstrates the financial strength that S&S Chemical has been able to continue to build.

Income Statements

The Historic Income Statement for S&S Chemical is attached as Appendix 4. This Income Statement details the dramatic sales and earnings growth that S&S Chemical has been about to develop.

The projected Income Statement is attached as Appendix 5. This projection only assumes 25% growth in our current business as well as the minimum Sales Quotas documented in the Sasol Wax Americas, Jeen International, and RAND Trading Distribution Agreements.

APPENDIX 1

Bruce Stevens Resume

Bruce Neal Stevens
25 Highland Place
Durango, Colorado 81301

SUMMARY PROFILE

Experienced Entrepreneur with proven development and management skills coupled with exceptional technical skills and significant exposure to manufacturing and commercialization projects. Excellent leadership skills with the ability to motivate a team to achieve and exceed specified objectives. Demonstrated ability to effect continuous process improvement, meet customers' needs, expand market share, grow earnings and increase shareholder value through management of others. Highly effective communication and people skills.

EXPERIENCE

VECO USA, Inc.
VECO USA is an engineering, procurement, and construction company that serves multiple markets.
Part Time Marketing Manager, Durango, Colorado **1/03 - present**
- Assists with Marketing Efforts on an as-needed basis to ensure longevity of Durango satellite office.

Four Corners Area Manager, Durango, Colorado **12/01 – 1/03**
- Successfully managed office staff and gained over $1 million dollars of new business per year.

Project Manager IV, Durango, Colorado **3/01 – 12/01**
- Successfully expanded office staff from 5 to 10 people within 2 months.
- Booked over $250,000 of new business within 3 months.

Primenergy, INC., Tulsa, Oklahoma
Primenergy is an engineering, procurement, and construction company that licenses patented biomass-to-energy technology that utilizes gasification techniques to convert such raw materials as rice hulls, poultry litter, sewage sludge, as well as other biomass materials into thermal energy and/or electricity.
Senior Process & Applications Engineer **2/00 – 3/01**
- Engineered and procured equipment for an olive oil waste to electricity plant with a 35% savings over planned budget.
- Identified and implemented several significant process improvements within 3 months of joining company that saved greater than $1.5 million.

S&S Chemical, INC., Tulsa, Oklahoma currently Durango, Colorado
S&S Chemical is a specialty chemical company that primarily distributes wax polymers into various markets.
Founder and General Manager **6/98 - present**
- Started up and continue to grow company.

Syntroleum Corporation, Tulsa, Oklahoma
Syntroleum Corporation is a technology company that utilizes Fischer-Tropsch, autothermal reforming and product upgrade processes for gas to liquids conversion.
Senior Process Engineer **12/97 – 1/00**
- Designed, engineered, constructed, and started up first-of-a-kind $20 million Gas-To-Liquids demonstration plant within 8 months.
- Researched, optimized, and commercialized a method which increased process efficiency by 65%.
- Designed, constructed, and started up new 3,000 sq. ft. pilot plant including 21 reactors.

Norit Americas, Inc, Marshall, Texas
Norit is a manufacturer of lignite and wood based activated carbon.
Production Engineer **2/97 – 11/97**
- Established production record of activated carbon while reducing production costs by 20%.
- Improved efficiency of Boiler and Wastewater treatment systems by 35% through optimizing process chemicals.

Petrolite Polymers Division
Petrolite is a specialty chemical company that produces additives which enhance the performance of numerous products across a wide variety of markets.
Strategic Projects Manager, Tulsa, Oklahoma **8/94 – 11/96**
- Led Division to 3 consecutive years of increased earnings resulting in an overall increase of 38%.
- Redirected Division from a technology driven company to a customer intimate, market driven company which allowed above achievement as well as significant future growth potential.
- Developed 5 Year Strategic Manufacturing Plan which saved Corporation over $25 Million.
- Identified an acquisition target and successfully positioned company for purchase by Petrolite.

Plant Manager – Clear Lake Plant, Houston, Texas **5/93 – 8/94**
- Increased productivity at Clear Lake Plant by 70% while maintaining a high quality standard.
- Reduced costs by 30%, on-the-job accidents by 40% and waste disposal by 80% by introducing Participative Management style and increasing employee involvement.

Production Manager – Kilgore Plant, Kilgore, Texas **11/92 – 5/93**
- Implemented Process Safety Management Standard throughout plant's 6 diverse operating units.
- Increased earnings by 40% by eliminating large off-spec inventory, increasing product yields and reducing operating costs.

Technical Manager, Kilgore, Texas **5/91 – 11/92**
- Identified and commercialized a method of oxidizing polyethylene waxes using air rather than oxygen which saved multi-million dollar product line after an industrial accident.
- Implemented ISO 9002 program in Quality Assurance and Product Research.
- Increased Quality Assurance productivity 60% by empowering employees, eliminating waste and setting goals.

Product Research Manager, Kilgore, Texas **9/89 – 5/91**
- Generated $5 million of new product sales by working with sales and marketing to identify customers' needs and then tailoring and commercializing new products to meet those needs.
- Led team which increased productivity of microcrystalline wax plant by improving process yields and implementing new process.

Dow Chemical Company
Senior Development Engineer – Polyurethanes Technical Service & Development **5/86 – 9/89**
- Identified and built a new multi-million dollar market for an existing product within one and a half years.
- Researched, developed and patented use of novel raw material to improve physical properties of final product.

Development Engineer – Hydrocarbons & Energy Research **5/83 – 5/86**
- Presented several papers at industry conferences and chaired subcommittees which adopted improved ASTM test methods.
- Developed oxygen blown coal gasification process and demonstrated its use at the pilot plant stage.

EDUCATION
M.S., Chemical Engineering, University of Oklahoma, Norman, OK, May 1983 (4.0 GPA)
B.S., Chemical Engineering, University of Oklahoma, Norman, OK, May 1982 (3.6 GPA)

PROFESSIONAL ASSOCIATIONS
Society of Professional Engineers
American Institute of Chemical Engineers

APPENDIX 2

Rick Nelson Resume

RICHARD NELSON

809 Kansas Street
Carol Stream, Illinois 60188

Home: 630/690-8084
Cell Phone: 847/373-8799

Email: rhn53153@aol.com

LOGISTICS • MANAGEMENT • CUSTOMER SERVICE • SALES

Strong, team-focused, consensus building leader, with multimillion dollar contributions to profit growth of global firm. Accomplished manager/mentor of staff, maximizing potential and facilitating both company and individual goals. Responsible fiscal manager, successfully negotiating contracts resulting in reduced budgetary costs.

PROFILE

- **Logistics:** Provided integrated services for product management, from procurement of raw material, to storage and transportation to customer. Resolve domestic and international customer service issues. Negotiated transportation rates for rail, leased tank car fleets and storage sites.

- **Management:** Effective in the supervision of staff. Analyzed human resources needs based upon company business objectives. Developed successful teams through staff selection, training, motivation, counseling and recognition. Promoted 28% of staff.

- **Process Improvement:** Refined logistics processes to comply with Total Quality Management resulting in division cost savings. Created greater efficiencies between matrixed teams and functions, by eliminating duplication and improving communication.

- **Sales:** Exceptional territory development centered upon customer service, new business development, vendor relations, and staff motivation, resulting in an increase of 42% in the active customer base. Intense cultivation of sales territory yielded a gross margin increase of 300%.

- **Fiscal Responsibility:** Managed vendors, contracts and sales based upon company fiscal goals. Monitored P & L ratio's, adjusted expenses accordingly.

PROFESSIONAL EXPERIENCE

BP Global Special Products, Skokie, Illinois July 1987 to July 2003
(Formerly Dussek Campbell and National Wax)

Logistics, Customer Service and Supply Manager Jan. 2002 to July 2003

- Managed procurement, logistics and customer service for the wax and cables divisions
- Supervised a staff of seven
- Reduced raw materials spending by 10% over previous year

Logistics, and Customer Service Manager..

Jan. 2001 to Jan. 2002

- Managed logistics and customer service for the wax division
- Reduced LTL freight costs an average of 25%
- Negotiated a new container rate from China reducing freight costs $36,000
- Supervised a staff of four

Territory Manager (19 states) and Logistics Manager April 1994 to Jan 2001

- Improved territory gross margin 42%
- Increased active customer base 70.5%
- Managed high-volume accounts from multiple sectors
- Negotiated all freight rates and managed owned/leased tank car fleet

Manager of Quality and Distribution April 1991 to April 1994

- Implemented Total Quality Management process
- Negotiated all transportation contracts and rates
- Managed customer service team
- Supervised staff of three

Distribution Manager July 1987 to April 1991

- Negotiated all transportation contracts and rates
- Manage customer service team
- Negotiated first rail contract for company, saving $400,000 annually

QO Chemicals, Inc. Sept. 1980 to July 1987
(Formerly the Chemicals Division of the Quaker Oats Company)

Supervisor Distribution Services

- Manage export activities
- Negotiate ocean container, parcel tanker, truck and rail rates

Distribution Specialist

- Prepared department budget
- Revamped hazardous material program

Distribution Analyst

- Negotiated first rail contract for company resulting in annual savings of $850,000

EDUCATION AND LEADERSHIP

Elmhurst College, Elmhurst, Illinois BS Business Administration 1984
Triton College, River Grove, Illinois AS Traffic and Transportation Management 1978

Member: BP GSP America's Senior Management Team 2003
Member: Wax Subcommittee of the National Petroleum Refiners Association 2003

Instructor: Triton and Oakton Colleges 1988 to 1993
Courses Taught: "Introduction to Transportation and Physical Distribution"
"Safe Transportation of Hazardous Materials"

APPENDIX 3

12/31/04 Balance Sheet

APPENDIX 4

Historic Income Statements

S&S CHEMICAL, L.L.C.
Historic Income Statement

S&S CHEMICAL CONFIDENTIAL - LIMITED ACCESS

	1999	2000	2001	2002	2003	2004
Gross Sales	$0	$0	$42,698	$599,466	$642,422	$1,220,652
Cost of Goods Sold	$0	$547	$37,762	$471,737	$511,780	$977,627
Gross Profit	$0	($547)	$4,936	$127,729	$130,642	$243,025
Other Income		$46	$63	$1,890	$466	$133,542
Gross Income	$0	($501)	$4,999	$129,619	$131,108	$376,567
Advertising					$559	$3,721
Car Expenses	$266			$23	$59	
Depreciation				$7,516		
Insurance				$712	$1,191	$4,111
Interest - Paid to Bank		$6,420				
Interest - Other	$36	$997	$6,189	$9,567	$6,278	$13,367
Legal and Professional Services	$3,285	$3,168	$2,819	$13,215	$88,404	$88,252
Office Expense	$79		$2,859	$769	$689	$6,933
Supplies		$14,752		$2,606	$620	$1,468
Taxes and Licenses			$228	$82	$612	$4,639
Travel	$1,452	$1,700	$3,748	$2,714	$7,616	$29,086
Meals and Entertainment	$702	$243		$102	$855	$3,984
Rent						$850
Utilities		$1,448				
Wages						$57,914
Other Expenses	$5,945	$57	$394	$27,301	$40,234	$50,322
Total Expenses	$11,763	$28,785	$16,237	$64,607	$147,117	$264,648
Expenses for business use of home				$1,483		
Net Profit	($11,763)	($29,287)	($11,238)	$63,529	($16,009)	$111,918
Year End Inventory				$81,194	$73,440	$309,433
2004 Expenses prepaid in 2003					$89,684	

APPENDIX 5

Projected Income Statements

APPENDIX 5

S&S CHEMICAL, L.L.C.
Projected Income Statement

S&S CHEMICAL CONFIDENTIAL - LIMITED ACCESS

	2004	2005	2006	2007	2008	2009
Gross Sales	$1,220,652	$9,923,733	$16,855,667	$22,233,640	$27,792,050	$34,740,063
Cost of Goods Sold	$977,627	$6,351,100	$10,635,350	$13,943,036	$17,428,795	$21,785,994
Gross Profit	$243,025	$3,572,633	$6,220,317	$8,290,604	$10,363,255	$12,954,068
Other Income	$133,542	$1,000	$1,200	$1,500	$1,900	$2,400
Gross Income	$376,567	$3,573,633	$6,221,517	$8,292,104	$10,365,155	$12,956,468
Advertising	$3,721	$8,932	$15,551	$20,727	$25,908	$32,385
Car Expenses		$4,644	$8,086	$10,778	$13,472	$16,840
Insurance	$4,111	$10,800	$12,960	$15,552	$18,662	$22,395
Interest	$13,367	$45,288	$54,346	$65,215	$78,258	$93,909
Legal and Professional Services	$88,252	$55,000	$66,000	$79,200	$95,040	$114,048
Office Expense	$6,933	$15,933	$19,119	$22,943	$27,532	$33,038
Supplies	$1,468	$2,000	$2,400	$2,880	$3,456	$4,147
Taxes and Licenses	$4,639	$98,247	$171,059	$227,992	$284,990	$356,237
Travel	$29,086	$214,358	$373,219	$497,436	$621,795	$777,244
Meals and Entertainment	$3,984	$1,286	$2,239	$2,985	$3,731	$4,663
Rent	$850	$10,200	$10,200	$15,300	$15,300	$22,950
Wages	$57,914	$388,000	$448,200	$538,610	$715,541	$751,318
Other Expenses	$50,322	$500,169	$870,844	$1,160,685	$1,450,856	$1,813,570
Total Expenses	$264,648	$1,354,857	$2,054,224	$2,660,301	$3,354,540	$4,042,745
Net Profit	$111,918	$2,218,776	$4,167,293	$5,631,802	$7,010,615	$8,913,724

Wages Detail						
Rick Nelson	$95,000.00	$150,000.00	$165,000.00	$173,250.00	$181,912.50	$191,008.13
Lab Supervisor		$40,000.00	$42,000.00	$44,100.00	$46,305.00	$48,620.25
Customer Service Representative		$32,000.00	$33,600.00	$35,280.00	$37,044.00	$38,896.20

S&S CHEMICAL, L.L.C.
12/31/04 Balance Sheet
Cash Basis

S&S CHEMICAL CONFIDENTIAL - LIMITED ACCESS

ASSETS		
Current Assets		
Checking/Savings		
Citizens Bank of Pagosa Springs		$522.77
Bank of Durango		-$21,759.33
CD Account		$26,454.69
Com. Bank & Trust		$21.00
Total Checking/Savings		$5,239.13
Accounts Receivable		
Accounts Receivable		$224,260.60
Total Accounts Receivable		-$25.06
Other Current Assets		
Inventory		$309,432.97
Total Other Current Assets		$309,432.97
Total Current Assets		$314,647.04
Fixed Assets		
Equipment		
Accumulated Depreciation	-$7,516.18	
Cost	$7,516.18	
Equipment - Other	$12,388.61	
Total Equipment		$12,388.61
Total Fixed Assets		$12,388.61
Other Assets		
Security Deposit		$850.00
Prepaid Retainer - Cornerstone		$450.00
Intangible Asset		$635.00
Loan Costs		$6,683.50
Accumulated Amortization		-$490.00
Total Other Assets		$8,128.50
TOTAL ASSETS		**$335,164.15**
LIABILITIES & EQUITY		
Liabilities		
Current Liabilities		
Accounts Payable		$364.00
Total Credit Cards		$37,032.78
Other Current Liabilities		
Current Position of L.T. Debt		$38,500.00
Total Other Current Liabilities		$38,500.00
Total Current Liabilities		$75,896.78
Long Term Liabilities		
SBA Loan Citizens Bank		$211,772.51
SBA Loan Bank of Durango		$36,410.70
Total Long Term Liabilities		$248,183.21
Total Liabilities		$324,079.99
Equity		
Member's Equity		
Draws	-$107,043.32	
Investments	$599.31	
Life Insurance	-$2,911.00	
Total Member's Equity		-$109,355.01
Retained Earnings		$8,520.91
Net Income		$111,918.26
Total Equity		$11,084.16
TOTAL LIABILITIES & EQUITY		**$335,164.15**

APPENDIX 5

Scheduler/Planner		$40,000.00	$42,000.00	$44,100.00	$46,305.00	$48,620.25
Accountant		$36,000.00	$33,600.00	$35,280.00	$37,044.00	$38,896.20
Sales Person 2		$90,000.00	$42,000.00	$44,100.00	$46,305.00	$48,620.25
Sales Person 3			$90,000.00	$94,500.00	$99,225.00	$104,186.25
Lab Technician				$36,000.00	$37,800.00	$39,690.00
Customer Service Representative 2				$32,000.00	$33,600.00	$35,280.00
Office Manager					$75,000.00	$78,750.00
Other Employee					$75,000.00	$78,750.00
Total Wages	$95,000.00	$388,000.00	$448,200.00	$538,610.00	$715,540.50	$751,317.53

Subject: Summary
From: "bruce stevens" <bruce.stevens@snschemical.com>
Date: Thu, 24 Mar 2005 20:32:36 -0700
To: <baderfa@execpc.com>

S&S CHEMICAL CONFIDENTIAL – LIMITED ACCESS

Dear Sir:

Thank you very much for going to the trouble to fax me your letter on confidentiality. I greatly appreciate it and hope I did offend you by sending the original Confidentiality Agreement.

Please find the attached Business Summary. I would greatly appreciate the opportunity to discuss it with you at your leisure.

I also look forward to receiving your autobiography.

Sincerely,

Bruce Stevens
S&S Chemical, Inc.
PO Box 2027
Durango, Colorado 81302

(970) 749-5304 phone
(970) 375-2816 fax

011105 Business Summary.doc	**Content-Type:** **Content-Encoding:**	application/msword base64

011005 Stmts for Business Summary.xls	**Content-Type:** **Content-Encoding:**	application/vnd.ms-excel base64

Subject: Review of S&S Chemicals
From: "Irwin klundt" <klundt@robsoncom.net>
Date: Mon, 21 Mar 2005 12:44:15 -0700
To: <baderfa@execpc.com>
CC: "Bruce Stevens" <Bruce.Stevens@SnSChemical.com>

Alfred;

Please note my new e-mail address.

I spoke with Bruce Stevens about your interest in reviewing the value of his company. He is interested in having you do this. He can be reached at the following e-mail address: Bruce.Stevens@SnSChemical.com
Phone: 970-749-5304

I have copied Bruce on this e-mail and will have him call you to make arrangements.

Bruce;

Dr. Alfred Bader can be reached at baderfa@execpc.com

Phone: 414-277-0730

I trust that this electronic introduction will prove fruitful

Please keep me informed of the outcome.

Best regards

Ike

38076 S. Arroyo Way
Tucson, AZ 85739
Phone: 520-825-4352
Klundt@robsoncom.net

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709
E-mail: alfred@alfredbader.com

A Chemist Helping Chemists

Fax to 970 375 2816

24 III 05

Dear Mr. [illegible],

I know nothing about S & S Chem. Co. (except what you told me today) and whatever I learn from you I will keep confidential — unless I receive your permission.

Best regards,

Alfred Bader

TRANSMISSION VERIFICATION REPORT

TIME : 03/24/2005 03:35

DATE,TIME	03/24 03:36
FAX NO./NAME	19703752816
DURATION	00:00:24
PAGE(S)	01
RESULT	OK
MODE	STANDARD ECM

S&S Chemical

P.O. Box 2027
Durango, Colorado 81302-2027

FACSIMILE COVER SHEET

Date: 3/23/05

To: Dr. Alfred Bader

From: Bruce Stevens

3 Pages Including This Coversheet

If you do not receive the number of pages indicated above please call (970) 749-5304.

Dear Sir:

Please find the attached, proposed Confidentiality Agreement we discussed yesterday.

I look forward to your reply as well as the potential opportunity to work with you.

Sincerely,

Phone: (970) 749-5304 Fax: (970) 375-2816

S&S Chemical
P.O. Box 2027
Durango, Colorado 81302-2027

March 23, 2005

Dr. Alfred Bader

Dear Sir:

In connection with an evaluation of strategic alternatives, S & S Chemical, Inc. ("Company" or the "Business") is willing to furnish Dr. Alfred Bader with financial and other information concerning the Business. As a condition to our being furnished with such information, Dr. Alfred Bader agrees to treat as confidential any Business information which is furnished to Dr. Alfred Bader by or on behalf of the Company (herein collectively referred to as the "Evaluation Materials"). The term Evaluation Materials does not include information which (a) becomes generally available to the public other than as a result of a disclosure by Dr. Alfred Bader or Dr. Alfred Bader's directors, officers, employees, agents or advisors; (b) is already in Dr. Alfred Bader's possession as shown by Dr. Alfred Bader's previous written records, provided that such information is not known by Dr. Alfred Bader to be subject to another confidentiality agreement with or other obligations of secrecy to the Company or another party; (c) becomes available to Dr. Alfred Bader on a non-confidential basis from a source other than the Company or its advisors, provided that such source is not known by Dr. Alfred Bader to be bound by a confidentiality agreement with or other obligation of secrecy to the Company or another party; or (d) is obligated to be disclosed pursuant to applicable law, regulation or legal process . However if Dr. Alfred Bader is required by law (pursuant to legal proceedings, subpoena, civil investigative demand, or other similar process) to disclose any Evaluation Materials, Dr. Alfred Bader shall notify the Company promptly in writing so that the Company may seek a protective order or other appropriate remedy.

In consideration for disclosure of the Evaluation Materials we acknowledge that:

(1) Although the Company will endeavor to include in the Evaluation Materials only information that is believed to be reliable and relevant for the purpose of Dr. Alfred Bader's evaluation, the Company makes no representation or warranty as to the reliability, accuracy or completeness of the information contained in the Evaluation Materials.

(2) Dr. Alfred Bader will not, without the prior written consent of the Company, disclose the Company's identity, the fact that the Company may be the subject of any transaction, the fact that the Evaluation Materials have been made available to Dr. Alfred Bader, or the contents of any Evaluation Materials, to any third party other than as

required by law or due process, except that any such information may be disclosed to those who agree to be bound by the terms of this Agreement. However if Dr. Alfred Bader is required by law (pursuant to legal proceedings, subpoena, civil investigative demand, or other similar process) to disclose the Company's identity, the fact that the Company may be the subject of any transaction, the fact that the Evaluation Materials have been made available to Dr. Alfred Bader, or the contents of any Evaluation Materials; Dr. Alfred Bader shall notify the Company promptly in writing so that the Company may seek a protective order or other appropriate remedy.

(3) Dr. Alfred Bader will return all Evaluation Materials to the Company and destroy all notes, reports and other materials prepared by or for Dr. Alfred Bader if the Company so requests.

(4) This Agreement shall be binding for a period of three (3) years from the date of execution. The Company reserves the right in its sole discretion to assign its rights and the enforcement thereof under this Agreement to a purchaser of the all or part of the Business. This Agreement is not assignable by Dr. Alfred Bader to any person or entity whatsoever without the prior written consent of the Company and any attempted assignment without such consent shall be null and void.

(5) This Agreement shall be binding upon Dr. Alfred Bader's successors and assigns and shall be governed by and construed in accordance with the laws of the state of Colorado.

(6) The provisions of this Agreement are severable and if any one or more of such provisions are determined to be void or unenforceable, in whole or in part, the remaining provisions of this Agreement shall nevertheless be binding and enforceable.

(7) This Agreement expresses the entire agreement of the parties with respect to the subject matter herein contained and all prior or contemporaneous agreements or negotiations are hereby superseded. This Agreement may be modified or amended only in writing signed by the Company and Dr. Alfred Bader.

If the foregoing correctly sets forth your understanding please indicate your agreement and acceptance in the space provided below and return one copy of the executed Agreement to the undersigned. Upon execution, this Agreement will become a binding Agreement between us as of the date of your execution.

Sincerely S & S Chemical, Inc.	Agreed and Accepted Dr. Alfred Bader
By____________________	By____________________
	Date ____________

Tel. 3/24 Too complicated.

Subject: Re: RE: Your letter]
From: "R. Sime" <rodsime@csus.edu>
Date: Fri, 17 Oct 2003 14:17:42 -0700
To: "Alfred Bader Fine Arts" <baderfa@execpc.com>

Thanks, Alfred, for forwarding MJ's letter. Now I know she got what I sent.
I'll have to think about whether I want to contact MJ again about her suggestion that I redo the Mt piece for their website. Perhaps she thinks the matter is settled with your letter. At any rate, I am glad she's publishing your letter . In a sense our mission is partly accomplished in that it's unlikely C&EN will contact Rife in the near future for another piece.
Good wishes to you,
Ruth

> ----- Original Message -----
> **From:** Alfred Bader Fine Arts
> **To:** Ruth Sime
> **Sent:** Friday, October 17, 2003 1:29 PM
> **Subject:** [Fwd: RE: Your letter]
>
> -------- Original Message --------
> **Subject:** RE: Your letter
> **Date:** Thu, 16 Oct 2003 17:42:10 -0400
> **From:** Madeleine Jacobs <m_jacobs@acs.org>
> **To:** "'Alfred Bader Fine Arts'" <baderfa@execpc.com>
>
> Dear Al,
> I have heard from Ruth Sime, but her points were very similar to yours. I'm not going to run all three letters.
> Madeleine
>
> Madeleine Jacobs
> Editor-in-Chief
> Chemical & Engineering News
> 1155 16th Street NW
> Washington, D.C. 20036
> Phone (202) 872-6310
> Fax (202) 872-8727
>
> -----Original Message-----
> From: Alfred Bader Fine Arts [mailto:baderfa@execpc.com]
> Sent: Thursday, October 16, 2003 5:22 PM
> To: Madeleine Jacobs
> Subject: Re: Your letter
>
> Dear Madeleine,
>
> I very much appreciate your reply of today and can certainly wait another two weeks or, for that matter, another two months.
>
> I am surprised that you have not heard from Professor Sime.

Best wishes,
Alfred

Madeleine Jacobs wrote:

> Dear Al,
>
> I want to respond to your letter, which I have just received by fax.
>
> I have received in the past two months no fewer than 250 letters to the editor, all of which take attention and which will eventually be "disposed of." I'm sure you understand that responding to readers and choosing letters are in addition to all my other many duties as editor.
>
> The letter on the "Polish joke", which you believe is relatively unimportant, was important because I received 10 letters with that same complaint from readers all across the country. Your letter, on the other hand, is the only one I received about the Meitnerium essay. You make many important points, and I do plan to publish your letter with a response from the author. She took a while to respond to your letter, but I now have both your letter and her response in hand. I'm planning to send you both copies. I don't want the "dialogue" between you and the author to go on endlessly. Yes, I am taking my time, but if your letter is important, it will be important in two more weeks.
>
> I don't consider you pushy or stubborn, but I do ask and beg for your patience and understanding. What must seem like an easy call to you to publish your letter is not easy when we are also constrained by space each week in the letters department due to a poor advertising situation related to the economic climate.
>
> Sincerely,
> Madeleine
>
> Madeleine Jacobs
> Editor-in-Chief
> Chemical & Engineering News
> 1155 16th Street NW
> Washington, D.C. 20036
> Phone (202) 872-6310
> Fax (202) 872-8727
>
>

Subject: Archibald Scott Couper
From: "Sella, Andrea" <a.sella@ucl.ac.uk>
Date: Wed, 30 Jul 2003 11:47:59 +0100
To: baderfa@execpc.com

Dear Dr Bader,

I am sorry that it has taken me so long to get back to you but various things have supervened.

I wonder whether you would still be keen to give your talk on Couper to a group of alumni and current members of the Department on the 21st of November this year. The plan would be for your talk to precede the pre-dinner drinks.

Incidentally, I came across this web page which shows a recent photo of Couper's house: http://www.lenzienet.co.uk/chem/couper.htm
What he would have made of the pet store.....

Best regards,
Andrea Sella
--
Dr. Andrea Sella
[redacted]

Ann: please place in

Attached

L. Skurský Brno, Feb. 8, 2002

Dear Dr Bader,

the copy of your letter (of Jan. 27) adressed to our Dean prompted me to enter into the matter (not in any tactless or rude mode). The preliminary results were two e-mail messages

The Dean will respond (or has responded?) your letter himself, of course.

Obviously, due to your mentioning my name in the letter sparkelt his inviting me for a discussion („working lunch"). He clarified to me his ideas of how he intended to help Prof. Potáček in his difficult task. I strongly believe that the Dean has chosen correct methods. At the beginning, Potáček might feel it) with a slight discomfort - like a sort of intrusion into his own domain - but, I am sure, that finally, he will understand it as a real help for his task. - In the task, where he was, perhaps, too much concentrated on his own (not un-limited, of course) methods and chances.

If I could try to philosophize, it might appear as a sort of remnant of a somewhat outdated style of directing the individual Departments (of org., inorg. etc. Chemistries). Unfortunately those historically rooted modes frequently tended to certain selfishness and less sense for cooperation.

During the period, started few years ago, when J. Jonas was the Dean (and the physicist Prof. Schmidt acted as the Rector), a new tendency was born. Newly found units, corresponding to the progress in science, have been established as selfstanding laboratories (independent from traditional „Departments". They had been created only when not solely apparatuses were available. The main prerequisite for their creation was the availability of top quality people for the head positions.

(You might remember Jonas' intention to create the „A. Bader laboratory of Mass Spectrometry": the tentative head was in sight). This one did not come into being but others, very prosperous ones, did.

– over –

One of these is the institution around Professors Koča and Sklenář. (The fact that both of them had passed the course of „General biochemistry" given by me, did not play any role, but this fact explains my pride over those young men, whom, until recently, I used to call „boys".) I have mentioned this laboratory in our recent telephone chat: I think that a cooperation of the to-be Loschmidt Professor and this new progressive laboratory (or rather „center") could be for a mutual benefit.

As an annex to this letter you find a copy of basic information taken from a brochure, issued recently by the Rector's office. (Rector Zlatuška will send you soon a complimentary copy of the whole brochure.)

In conclusion I express my persuation (not only a hope), that the problem will be solved in not too distant future.

I suppose you do not object when, occasionally, I express my personal oppinion on matters in which I have <u>absolutely no executive</u> potency.

Accept, please, my wish of every good and „einen höflichen Handkuss für die Gnädige Frau". – I have no idea whether this (also here) practically forgotten politeness does (or did) have any English equivalent. – I hope Dr Isabel will pardon me.

Yours very sincerely

L. Skursky

Schneider, Audrey

From: Alfred Bader Fine Arts [baderfa@execpc.com]
Sent: Thursday, September 18, 2003 3:18 PM
To: Schneider, Audrey
Subject: [Fwd: Fw: Lieben-Award] FOR ALFRED BADER

-------- Original Message --------
Subject: Fw: Lieben-Award
Date: Wed, 17 Sep 2003 23:28:35 +0200
From: "RobertROSNER" <RobertRosner@everyday.com>
To: "Alfred Bader" <Baderfa@execpc.com>

----- Original Message -----
From: Arnold Schmidt
To: Robert Rosner
Sent: Wednesday, September 17, 2003 8:43 PM
Subject: WG: Lieben-Award

-----Ursprüngliche Nachricht-----
Von: Arnold Schmidt [mailto:arnold.schmidt@tuwien.ac.at]
Gesendet: Mittwoch, 17. September 2003 16:20
An: ' Robert Rosner (robert.rosner@everyday.com)'; ' Robert Rosner (robert.rosner@netway.at)'
Betreff: Lieben-Award

Lieber Bobby,

vor mir liegt eine weite Modifikation der Vereinbarung über den Liebenpreis. Es gibt folgende Änderungen:

1. Die Bezeichnung der Wissenschaftsgebiete lautet jetzt: ~~molecular medicine~~; molecular biology, chemistry, physics. Sowohl Peter Schuster als auch ich sind damit einverstanden.
2. Das Minimum der im Ausland tätigen Mitglieder des Auswahlkomitees wurde von drei auf zwei reduziert. Froh bin ich darüber nicht, aber Schuster hat mir versichert, dass die ÖAW schon damit gewisse Schwierigkeiten hat. Ich denke man sollte – mit leisen Knurren - zu stimmen.
3. Die Verleihung des Preises wird heuer in einer eigenen Zeremonie stattfinden, in den Folgejahren aber Teil der jährlichen Preisverleihungen der ÖAW. Das Wort „Special“ ist noch in Klammer gesetzt. Nach einigem Nachdenken bin ich aber jetzt dafür es zu streichen. Der Preis ist so außergewöhnlich, dass er ohnehin die Feier dominieren wird. (Für heuer ist es natürlich wichtig, dass es eine spezielle Veranstaltung gibt – und so ist es jetzt auch festgelegt).

Ich denke Bader sollte jetzt abschließen.

Liebe Grüße,
Arnold

P.S.: Ich habe diesen letzten Entwurf nach einem Gespräch mit Schuster als Fax direkt von der ÖAW erhalten. Frau Moser hat ihn auch an Bader geschickt. Leider habe ich vergessen: hast du ein Fax? Wie kommst du sonst zu dem Papier?

Schneider, Audrey

From: Alfred Bader Fine Arts [baderfa@execpc.com]
Sent: Thursday, September 18, 2003 3:19 PM
To: Schneider, Audrey
Subject: [Fwd: Vertragsentwurf] FOR ALFRED BADER

-------- Original Message --------
Subject: Vertragsentwurf
Date: Wed, 17 Sep 2003 23:30:05 +0200
From: "RobertROSNER" <RobertRosner@everyday.com>
To: "Alfred Bader" <Baderfa@execpc.com>

Lieber Alfred,
Wahrscheinlich bekommst Du in den nächsten Tagen den Vertragsentwurf von der Akademie mit einigen Änderungsvorschlägen.Aus der E-mail vom Arnold, die ich an Dich weiterleite, siehst Du sein Kommentar dazu. Zu Punkt 3 habe ich noch einmal mit Arnold und mit Chriistian telefoniert. Christian wuerde sehr viel wert darauf legen, dass die Lieben Preise nicht nur 2004 sondern auch spaeter bei einer eigenen feierlichen Veranstaltung vergeben werden und nicht gemeinsam mit den anderen Preisen der Akademie. Arnold glaubt, dass wenn Du schreibst, dass Du die "special ceremony" , als wichtig betrachtest, die Akademie nachgeben wird Vielleicht kannst Du schreiben, dass Du die Akademie ersuchst, in Anbetracht des besonderen Charakters der Lieben Stiftung, in der ausdruecklich auch Wissenschaftler beruecksichtigt werden,die nicht in Oesterreich arbeiten, ihren Standpunkt zu überdenken und einer special ceremony zuzustimmen. .Vielleicht kann man der Akademie entgegen kommen, dass man "special ceremony" mit einem Ausdruck "bis auf weiteres" einschränkt. Ich weiß nicht ob das auf Englisch "until further notice" heißen kann
Wenn Du mit Arnold telefonieren willst, kannst Du ihm am Besten mit seinem cell phone erreichen. Da gibt es eigentlich nie Probleme.Die Nummer ist:0699-11-33-75-32
Liebe Gruesse
Bobby

(h)

This message scanned for viruses by Corecomm

(h) · 485 4162
(o) 58801 38710

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

January 3, 1996

Dr. Jean Cooley
Research Associate
Syncrude Canada Ltd.
Edmonton Research Center
10120 - 17th Street
Edmonton, Alberta T6P 1V8
Canada

Dear Dr. Cooley:

Your thoughtful letter of December 20th arrived here only yesterday and gave me a great deal of pleasure.

As you will be able to imagine, I have lectured at a great many places, and nowhere was treated more kindly than you treated Isabel and me. And now I can tell you that I have never seen such informative and amusing reviews of my talks.

I am happy that you read my autobiography. Might you consider writing a book review for the *Canadian Chemical News* or perhaps suggest that to one of my oldest chemist friends, Professor Norman Jones? After all, the book is very much in part a Canadian story and might well be of interest to Canadian chemists.

With all good wishes for 1996, I remain,

Yours sincerely,

AB/cw

75th CSC Conference Lecture Series

December 20, 1995

Dear Dr. Bader

I have enclosed copies of the reviews from the five lectures you gave in Edmonton as our 75th CSC Conference Lecturer. Infochem is a newsletter which we publish for the CIC members in the Edmonton area. It lets our members know of upcoming events and includes reviews of past events. I think the reviews of your talks are excellent. I have also included a piece by Stan Backs on Chemophobia on Children's Television since he relates this review to your talk.

This summer I read your book and thoroughly enjoyed it. I could hear you relating those stories to us in your lectures as I read them in your book.

Many thanks to you and Mrs. Bader for coming to Edmonton and presenting these lectures. I hope you will both enjoy the upcoming festive season.

Sincerely

Jean cooley

Jean Cooley

ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

May 5, 1993

Mr. Michael Carroll
Sourcing Manager
Puchasing Department
Sandoz Chemicals Corporation
4000 Monroe Road
Charlotte, North Carolina 28205

Dear Michael:

Just a note to wish you the very best in your new position.

Sandoz is a great company.

Sincerely,

By Appointment Only
ASTOR HOTEL SUITE 622
924 EAST JUNEAU AVENUE
MILWAUKEE WISCONSIN USA 53202
Tel 414 277 0730 · Fax 414 277 0709

Somatocor

Innovative Somatostatin Therapies

Company Mission

- Somatostatin Drug Pipeline
- First orally active Somatostatin drugs
- New valuable non-CNS indications for oral drug
- First Somatostatin CNS therapeutic

Expertise and Consultants

➢ Gideon Shapiro	Innovator, Drug Design (Somatocor)
➢ Eugene Woltering	Clinical Oncologist (LSU Medical Center)
➢ Indu Parikh	DrugDelivery (RTP Pharmaceuticals)
➢ Joost Van Bree	Pharmacokinetics (Pepscan)
➢ Stefan Borg	Regulatory Affairs(Copharos Pharmaceuticals)

Today’s $500MM Somatostatin Market

- Sandostatin and Sandostatin LAR (Novartis)
- Octreoscan (diagnostic imaging agent, Novartis)
- Vapreotide (Ipsen-Beafour)
- Lanreotide (DebioPharm)
- All products peptides

Limitations of Today's Somatostatin Peptide Drugs

➢Administration	Subcutaneous or I.V. Injection
➢Duration of Action	Short Half Life
➢Dosing	Low Concentration
➢Cost	High Cost
➢Bioavailability	No Brain Penetration, no CNS therapeutics

Somatocor's Peptidomimetic Somatostatins

- ➢10years of Preclinical Research Data at Sandoz/Novartis
- ➢PCT Patent filed May 2001 (Novartis)
- ➢Library of Potent Analogs
- ➢Leading Know-How in Somatostatin Drug Design

Somatocor’s Small Molecule Advantages

➢Administration	Oral
➢Duration of Action	Long Half Life >10hrs
➢Dosing	High Daily Dose Capability
➢Cost	2$ dose
➢Bioavailability	accessible to CNS

Somatostatin Structure and Biology

➢Somatostatin (SRIF)	14-amino acid endogenous peptide hormone
➢General Biological Function	Inhibitory Factor (eg. of Growth Hormone Release)
➢Sandostatin (octreotide)	8-amino acid Somatostatin analog with metabolic stability
➢Pharmacophore	beta 2’ turn structure, Phe-Trp-Lys amino acids
➢Somatostatin Receptors	5-subtypes sstr1, sstr2, sstr3, sstr4, sstr5
➢sstr2 receptor	most relevant to clinical effects of Sandostatin

Small Molecule Somatostatin Mimics

- ➢Over 1,000 Analogs Synthesized over Decade at Sandoz
- ➢Structure Based Drug Design for Beta turn Pharmacophore
- ➢New Class of Highly Potent Small Molecules Discovered
- ➢Lead Candidate for non-CNS indications = SCR-007
- ➢Lead Candidate for CNS indications = SCR-498

SCR-007 Chemistry

➢Synthesis	simple synthetic route
➢Scale-up	10gram to date, amenable to manufacture
➢Salt form	Hydrochloride
➢Stability	stable in salt form to storage
➢Chirality	One chiral center, racemate

SCR-007 Pharmacology

➢High Potency	Subnanomolar, microgram-milligram doses
➢High Selectivity	100-fold for sstr2 vs sstr receptors
➢Preclinical Efficacy	Rat, Monkey (Growth Hormone inhibition)
➢Biovailability	2% oral bioaviability from 3mg/kg ED50
➢CNS Penetration	poor

SCR-007 Safety (10mg/kg Oral)

- ➢No lethality observed
- ➢No overt cardiovascular effects
- ➢No overt motor or behavioural effects

Pharmacokinetics

- Rat ADME study for radiolabeled analog SCR-498
- Oral Bioavailibility 2% due to modest resorption
- Two compartment behaviour, 1st half life= 45min, 2nd = 20hrs
- No first pass effect, little metabolism, hepatic excretion of parent drug

Development Plan for SCR-007

- Develop effective for preclinical safety and efficacy
- Obtain IND approval for Phase I clinical studies
- Phase II study for bioequivalence to Sandostatin
- Parallel development of higher bioavailability formulations

Product Pipeline

➢Oncology	High dose regimen inhibiting angiogenesis
➢Transplantation	Coadministration with Sandimmune
➢Gastrointestinal	Irritable Bowel Syndrome

Drug Pipeline

- Somatostatin Drug Pipeline
- First orally active Somatostatin drugs
- New valuable non-CNS indications for oral drug
- First Somatostatin CNS therapeutic

Development of CNS Therapeutics

- ➢Screen existing library of compounds
- ➢Synthesize CNS active drug candidates
- ➢Select lead analog from class eg. SCR-498
- ➢Characterize efficacy in epilepsy and mental health models
- ➢Preclinical safety studies

Financing Needs and Exit

- $3-5MM for 2001-2003 per IND
- $30-50MM for 2003-2005 Phase II clinical
- Novartis Bioventure Fund evaluating investment
- IPO or sale of company for >$100MM by 2004

April 9, 2001

Gideon Shapiro
5507 NW 80th Ave
Gainesville, FL 32653
Ph. 352-256-6673

Alfred Bader
Suite 622-Astor Hotel
924 E. Juneau Avenue
Milwaukee, WI 53202
Ph: 414-277-0730

Dear Dr. Bader,

Please find enclosed information for Somatocor, the company I am founding to treat conditions of unmet medical need in oncology, and CNS diseases. It is based on a class of novel sulfonyl hydantoins. These molecules perfectly mimic the beta-turn pharmacophoric structure present in the endogenous inhibitory neuroendocrine peptide hormone somatostatin. I invented these compounds at Sandoz in a decade long project to create orally active mimetics of Sandostatin. Sandostatin is an injectable stabilized peptidergic somatostatin drug that is now the therapeutic of choice for treating neuorendocrine cancer patients, and severe diarrhea often encountered in many disease states e.g. for cancer patients undergoing abdominal radiation therapy. Clinical efficacy for somatostatinergic therapy is proven in many other disorders including diabetic retinopathy. Unfortunately, the potential therapeutic benefits of Sandostatin, including the treatment of a far broader range of cancers, are circumscribed by the fact that it is expensive and must be injected.

Several compounds from the peptidomimetic project were equipotent to Sandostatin in vitro and in vivo when applied subcutaneously. However, upon the merger the entire project group was disbanded after a decade of research without ever sending a drug with optimized oral activity into development. I firmly believe that valuable therapeutics can be developed from this novel class of molecules. I expect a very good safety profile since there is no acute toxicity and very little metabolism of the drug. Today there are several new drug formulation technologies for improving drug bioavailability. Since an efficient convergent synthesis is used, the drug can be mass produced. Therefore, physicians will prescribe more generously and consider testing in other indications such as high dose angiogenesis inhibition for vascularized tumor therapy that is currently cost prohibitive. In addition, Sandostatin does not penetrate into the brain so that patients with CNS diseases. Potential drug candidates from the class have been shown to enter the brain and usher in a new class of somatostatinergic CNS therapeutics to complete those for classical CNS monoaminergic neurotransmitter therapeutics. Epilepsy is the first indication likely to be treatable with somatostatin therapy based on preclinical research. Almost 50% of epilepsy etiologies are untreatable with current drugs, the aging population is creating a large growth in this set of patients. I

believe a depot monthly applied formulation of a particular drug from the class will be effective in improving the quality of life for these patients.

Last year Novartis research management approved outlicensing of the compounds. Since they already have a somatostatin drug, the risk of developing a follow on put it at low priority relative to new projects. Therefore, I now have the opportunity to realize a considerable advance in medicine. Novartis is filing the PCT patent covering at my request in May. I may then secure a license to the patent from Novartis. The starting capital required to get the first compound to Phase I clinical studies is estimated at $3-5MM. My past experience has shown that raising this capital may take anywhere from 6-months to 1 year. The new Novartis Bioventure Fund has started their evaluation process and will be the first step in the process. Currently, I require capital on the order of $100-200K to set up the company and be able to operate while securing the larger investment under reasonable terms. This will also go to setting up a chemistry lab to make the initial batches of drug and start process optimization for outsourcing the synthesis of larger GMP batches for toxicology. This is beyond my personal means with the exception of my EraGen stock which I would be willing to trade for the starting capital. I would welcome any advice you have on proceeding to start the company and your interest in making an investment in any way that could help get the company started and hire a chemist.

With my Best regards,

Gideon Shapiro

Gideon Shapiro

LSU Health Sciences Center
SCHOOL OF MEDICINE IN NEW ORLEANS
Department of Surgery

School of Medicine in New Orleans
School of Medicine in Shreveport
School of Dentistry
School of Nursing
School of Allied Health Professions
School of Graduate Studies
Health Care Services Division

Dr. Gideon Shapiro
5507 NW 80th Avenue
Gainesville, FL 32653

March 20, 2001

Dear Dr. Shapiro,

In response to your inquiry into the medical need for an orally active analog of Sandostatin, I believe that there is no question that clinicians will generally embrace such a drug for treatment of neuroendocrine tumors. Sandostatin must be injected several times a day due to its relatively short duration of action. This causes considerable patient discomfort in the patients we treat. The newer Sandostatin LAR also has significant drawbacks and has not diminished the use of Sandostatin itself. Although the long acting LAR formulation is injected once every three weeks, the dose cannot be readily adjusted. LAR also causes considerable irritation at the site of injection and this formulation also sometimes solidifies in the syringe. Furthermore, the potency of LAR seems to be attenuated by a neutralizing immune response to this formulation.

I would greatly look forward participating in the clinical testing of the orally active Somatocor drug as soon as the preclinical studies are completed. While suboptimal I do not believe you should be overly concerned with the absolute magnitude of the oral bioavailability. As long as the drug's potency is subnanomolar, an oral bioavailabilty of 2% in rats will not preclude the drug's viability in humans. The therapeutic window for Sandostatin is quite broad so that variability would not be expected to cause problems due to pharmacodynamic effects. It would, nevertheless, be advisable to formulate the drug for increased resorption since you know that the first pass effect is not significant.

Clinicians such as myself are looking for a drug that could be given once a day in oral form. The long half life of Somatocor's drug would be a big advantage and should enable us to better treat patients that require high dosing regimes for efficacy. High dose treatment may also broaden the application of the drug to other non-neuroendocrine tumors not treatable with Sandostatin. Animal studies in my lab have shown that Sandostatin is a potent angiogenesis inhibitor (mediated by the sstr2 subtype). Angiogenesis inhibition to starve the blood supply of solid tumors probably requires much higher doses (>10X) of Sandostatin to be given chronically in patients. This is cost

prohibitive today but could be addressed if your drug could be sold at a much lower per unit price. Finally, my colleagues conducting studies in GI indications will welcome the opportunity to use an orally active Sandostatin, particularly in chemotherapy-induced diarrhea dumping syndrome and a variety of other hypersecretory and hypermotility states where an injectable has serious compliance problems

It is good to see that advances are being made to orally active medicines in this extremely important class of drugs that I have investigated over the past 15years. I will be glad to act as a reference for you and hope to soon be among the first clinical investigators to work with an orally active somatostatin-like compound.

Kindest Personal Regards,

Eugene A. Woltering, M.D., F.A.C.S.
The James D. Rives Professor of Surgery and Neuroscience
Chief, Section of Surgical Endocrinology
Director of Surgical Research

CARCINOID SYMPOSIUM
SARASOTA, FLORIDA
May 11, 2000

"THE ROLE OF SANDOSTATIN ANALOGUE IN THE REDUCTION OF TUMOR GROWTH"

Presented by **Eugene Woltering, M.D.**
Louisiana State University Medical Center, New Orleans, Louisiana

It's all in the packaging, guys. Can we sort of move the projector, Bill, so that slides get on there. It probably got jostled during the meeting.

I'd like to sort of start at the beginning. You know, an expert is somebody who's at least one time zone away from home and has a of carousel slides. That means, Dr. Kvols, even though you had two carousels of slides, you're not an expert cause you're still in this time zone. And, Dr. Warner, I don't know how many slides you got. But I'm one time zone away and I got one carousel of slides.

Somatostatin and analogues are, as Dr. Kvols pointed out so eloquently, and this slide is a blatant rip-off of Larry's original slide with the little circles. This is native Somatostatin; this is what you and I make in our body every minute of every day of every hour. Somatostatin is, as Dr. Kvols pointed out, the universal off switch. I always say to my residents and interns, if you are in an exam and they ask you what turns something off and it has to do with the gut, answer Somatostatin and you'll be right 99 percent of the time. But as Dr. Kvols pointed out, this is the perfect control substance if you were the big guy upstairs designing a control mechanism, you'd design it this way. I'll give you an example. You eat a hot fudge sundae, your blood sugar goes up, you make insulin to bring your blood sugar back down. Everybody knows that. Ever ask yourself the question—what turns off the insulin so your blood sugar doesn't keep going down. The answer is Somatostatin. It's released as a peak. It goes up very rapidly and two minutes later it's gone. The off switch turns off the insulin and then it's gone. Why? Because you may decide, if you're my size, to eat a second hot fudge sundae ten minutes later. So you want to be able to turn off the second bout of insulin. That's perfect. You make it every second of every day in your body. It's not perfect if you want to use it as a drug. People in the early 1980's, shortly after Somatostatin was discovered and the sequence of these amino acids, elucidated by a group called Gillyman and Brizeau out of Texas, started to use Somatostatin. The good news is Somatostatin, if you use it intravenously by a continuous infusion, will suppress peptides, serotonin, all the things that Dr. Kvols and I and Dr. Warner will be talking about. That's the good news. The bad news is, is that you have to keep that IV drip going. So people weren't able to get out of the hospital. They had control of their symptoms as long as the IV was running, and then the really bad news was, when you pulled the IV, not only did things go back to where they were, they actually got worse. It's something called a rebound phenomenon. Within two weeks of the discovery of the sequence of these amino acids, the story goes that a man named Yannos Pless designed a mini-Sandos, mini-Somatostatin analogue. This is what we now know as octreotide or Sandostatin and what Dr. Pless did was cut the middle out of the

native molecule, kept these four amino acids that he thought was where this molecule bound to the receptor and added an alcohol on to the end of the molecule and amino acids come in D and L forms. The D forms are resistant to degradation in the body, so he added a D form here. That accomplished two things. The first of which is it made about 100-fold increase in its potency. That was pretty good, but that wasn't the really good news. The really good news is, this has a duration of action in the circulation measured in minutes, this has a duration of action or a half-life of about an hour and a half to two hours. This is one and a half to two minutes. So that you are 100 times more potent but you were also about a log order more able to keep it in the systemic circulation. That meant that you could give three or four shots of octreotide a day by sub-q and get out of the hospital and, you know, get back to the activities of daily living. While Novartis has sponsored this conference and has been a long-term supporter of all of us in here, there are other analogues that are coming to market. one is known as RC 160 or Vapriotide. It is now close to being marketed, I hear, in Europe. And another one that I don't have a slide of is called Lanriotide, which is on the market in Europe. Octreotide comes in two forms, as most of the people in this room know. A subcutaneous form called the aqueous form and one put into micro spheres that slowly release called LAR. How you structure one of these molecules is really critical. This is octreotide. This is a compound down here made by Dr. Pless and all he did was change this lysine to an ornathene and this is an important molecule to remember because I'm going to use it later in some of my studies to show that this molecule, while everything looks just about like this molecule, this won't bind to the receptor and is biologically inactive. Somatostatin came into the forefront because it suppresses peptides. Peptides are of amino acids and you heard Dr. Kvols talk about gastrin, insulin, somatostatin itself is a peptide, there are other ones—VIP, neurotensin, substance P, a list that goes on for about forever. When I was at Ohio State, one of my original teachers was a gentleman named Dr. Robert Zalinger. And Dr. Robert Zalinger is the surgeon who first discovered that tumors had functional capabilities. That is, they could make a substance that's normal in you and me. You and I make gastrin every minute of every day; it's what runs the acid-making part of our stomach. Gastrin binds to a cell called a parietal cell, and that parietal cell in the stomach makes acid. If you have a tumor that makes gastrin in boatloads, it is called a gastronoma—a tumor that makes gastrin. That's how all these tumors are named. It also is known by something called the Zalinger-Ellison syndrome. Just to give you a little insight into my life—I was the youngest member of the faculty at Ohio State after I finished my fellowship and joined the faculty, and Dr. Zalinger was the oldest. He was by that time in his early 80's. They didn't have any room in the Department of Surgery for Dr. Zalinger's office or my office, so we got moved right across the street to the Medical Library building. So it was Dr. Zalinger, myself, our two secretaries, and an empty floor. So Dr. Zalinger and I got to know one another pretty well. The first paper I ever wrote at Ohio State was taking one of this gastronoma tumors out in the operating room and chopping it up into single cells and then looking at what we could do to turn on and turn off gastrin release. So Dr. Zalinger nicely, after I got this manuscript all written up, agreed to review it for me. I gave it to him and the next day I am in my office sitting there talking to a family whose son is dying in the ICU and no knock on the door, the door opens, Dr. Zalinger throws the paper across the room and says "Woltering, you are the dumbest SOB I've ever met. If I could get your mother's phone number, I called her and tell her you are the dumbest SOB I ever met." So, with that, I got really interested in Zalinger-

Ellison syndrome. And we started, when I went to Oregon, a study where we used Somatostatin analogues in patients with gastrin-producing tumors or gastronomas.

Now, let's just review a little bit of what won a gentleman named Sutherland the Nobel Prize. Dr. Sutherland showed that a peptide, or in his case amines, could bind to a receptor that sits on the outside of a Imagine a cell as like a beach ball. And this is a revolving door in the beach ball. Well, at the time that Dr. Sutherland described this, the door didn't revolve, it was just a, you bind to it and it was like a light switch that turned on the lights inside of a cell. And those lights, or activities, are called signal transduction pathways. Big fancy doctor words for saying that when you plug in a lamp into the receptor, the receptacle in the wall, suddenly there's light. Well, it's the same kind of concept. A peptide binds to a receptor. Down deeper in the membrane there's an affecter. That affecter, in big doctor words, is called the G protein. When this complex all gets hooked together, this G protein tells complex pathways or signal transduction mechanisms inside the cell to do things. And those messages control things like secretion of peptides. Let's say this is serotonin or gastrin or whatever. Somatostatin binds to the receptor, the receptor talks to the G protein, the G protein talks to all these signal pathways, and they tell stop packaging and releasing the peptide, gastrin or serotonin. That's how Somatostatin was thought to work. That is a very small part of a story that is now getting much more complex that we'll go into more later, but Dr. Kvols alluded to it. Instead of it just being a plug in the receptor, what happens is this now is known to act like a revolving door. You put Somatostatin on its receptor, this receptor lygand the complex or peptide receptor complex, now can turn around like a revolving door and drop the Somatostatin inside the cell. For a long time everybody thought that Sandostatin went inside the cell and went to a lysesome. Now Dr. Kvols talked about that. A lysesome is another word for garbage disposer. Lysesomes give off enzymes that chew up the peptide into its amino acids and spit them back out so the body can use them to build something else. Recently we've discovered that there is another source of where these peptides go, and that is, they go to the nucleus, the nerve center of the cell, get inside the nucleus, and actually bind to DNA directly. There is a small section of DNA that the Somatostatin binds to.

That having been said, I'll turn back the clock to when I first went to Oregon, and Dr. Bill Fletcher, my partner, and I took patients with gastronomas and we gave them, we started them on 100 micrograms of Sandostatin three times a day and then we watched how their gastrin level was affected. And, as you can see, remember there's a break here, many of these people brought their gastrin levels down into normal ranges. Some very interesting patients. This patient had a very nice response, stopped her drug, we saw her back, we restarted her on the drug, when we saw her back, her gastrin level had normalized. This patient here had progressive metastatic disease and ultimately died of her disease. This patient here in the blue line did very well for about five years, and you'll see her in a minute when she had a single isolated recurrence in her liver. This patient here was a surgical cure at this point. So Somatostatin analogues, even in very low doses, had an effect on circulating peptide levels. Just like the people who had discovered Somatostatin would have predicted. However, like everything else, as you start to study people, looking for one problem or one effect, if you're smart and the gods look on you in a nice favorable fashion, they send you other observations that take you off on a whole new tangent in your life. One thing is very important and that is that we all recognize that none of us in this

room who are physicians do this alone. We all have residents, fellows, nurses, and a whole bunch of support staff that I'll try to remember to acknowledge as we go along. This is a patient who weighed about 450 pounds. This lady had a gastronoma, she had been treated with everything known to man. She had been given renal failure with the drug Streptozotocin. She had been treated with every combination of anti-diarrheal medicines known to man. Her son was a pharmacist in Boise, Idaho, and he heard that we had the Sandostatin trial for gastronomas available. She came over to Portland from Boise, Idaho, and we started her on Sandostatin. We kept her in the hospital in the GCRC for a couple of days. She had been having 30 bowel movements a day with her gastronoma. While she was massively obese, she was very active in her church, and that's all she wanted in life was to get a drug that would stop her diarrhea so she could go back to doing her church activities. Within three days she was down to having a bowel or two a day, she thought we were wonderful, and she toddled back off to Boise, Idaho. We didn't see her back for about 10 months. Her son called me every month and said how she was doing. We had a physician there who was doing her follow-up studies, etc. And so, when she came back in 10 months, she was in wonderful symptom control, still having a couple of bowel movements a day and thought we were wonderful. I wanted to send her home. My fellow Everett Mozel, who is now a surgeon in Salem, Oregon, said, "Gene, we ought to get a CAT scan." "Why do we need a CAT scan, Everett?" "Well, we oughta because, you know, she's doing so well, you know, we ought to see how bad her tumor is." Because she had just boatloads of tumor in her liver the first time we CAT-scanned her. Well, I don't see why we should spend $1500 on a CAT scan, but Everett said, please, boss, get a CAT scan. Well, listen to your friends because that's why you're friends. I'm sorry that the lights are so bad in here but this is her original CAT scan; there's a tumor here, a tumor here, a tumor here, a tumor here, her stomach is very thick, and on other cuts of her CAT scan she had a primary tumor in the pancreas that was about nine centimeters. This was before therapy, again a therapy only designed to be like very high-priced limodal to stop her diarrhea. When she comes back, this is in 1989, this case was first published, she had a complete tumor response. Biochemically, she had a complete response as well, normalized her gastrin for five years. This lady, like I said, was of the large economy variety, and also had very bad heart disease. And ultimately died five years later of a massive myocardial infarction, and an autopsy had a single isolated tumor right here five years later. Her pancreatic tumor had completely disappeared. And this was our first evidence that Sandostatin or octreotide acetate could affect tumor growth. And the question then was how did that happen. And our first thoughts were that, if you trapped these vesicles of peptide inside of a cell, could you give the cell peptide constipation to the point that it would get impacted and sort of blow up. Well, we could never prove that but it was a nice sort of idea that, you know, as a retribution against diarrhea that, you know, we'd give the cells constipation. But that never panned out. And then there was this funny guy named Kvols that I met just about this time who came out with the slide that you have already seen earlier this morning. And that is, that patients treated with chemotherapy who had carcinoids did very, very poorly but patients who had been extensively treated, who were put on octreotide acetate, had three times more survival time than people treated with chemotherapy. Again, how does a drug that's designed to be a symptom drug have any effect on tumors? And, at this point, which was in 1993, and this article by Larry in Actaancologic in 1993, single best carcinoid paper ever written, my hat's off to Larry Eiten, to

this day no one has ever written a better paper. But anyhow, this paper was the impetus for us to go a totally new way in my whole career and the research done in our laboratory, trying to figure out how the heck a drug designed to control diarrhea and flushing had anything to do with tumor growth. About the same time that we published the article about Shirley, and Dr. Kvols was doing his seminal work at the Mayo Clinic, there was a consensus conference at the NIH. When the NIH doesn't know what to do with a problem, they bring together all the experts who don't know what to do with the problem, and I can tell you they didn't know what to do with the problem because the bottom line of this consensus conference was, yeah, there are some people that have tumor responses to Sandostatin but there are not enough of those to really make it worthwhile. And the bottom line here is, all oncologists, let me just tell you, the magic number is that 50 percent of the people don't have, or the tumors don't shrink by 50 percent, you don't have a "objective response." Well, only about 13 percent of people had objective responses when put on octreotide acetate. However, what we all missed, and raise my hand and say I missed it too, was the other column here. Is that in 63 percent of those people their tumors seemed to just stop growing. Well, 13 percent is not a very impressive number; if you add 13 and 63, now you're saying, maybe 70 or 80 percent of patients treated with octreotide, and this is in the dark days, the ancient days of octreotide, very low doses used in these days, 80 percent of people, 70 percent of people, had some kind of tumor effect, as Larry pointed out on the previous slide.

Well, every time, if you're like me, you try to read about the subjects you're interested in and I had a good friend, another surgeon, believe it or not surgeons do do research, this is a guy named Colin Weber, and he was in Philadelphia, he is now at Emory in Atlanta, and Colin got interested in octreotide but not in carcinoid, interestingly enough. His interest as a cancer surgeon was in breast cancer. And Colin took nude mice, and you'll hear the term 'nude mice.' A nude mouse is a mouse that has been bred not to have any immune responses. So I can put an orangutan tumor or a human tumor in a nude mouse and it will grow. It will not recognize human as foreign. So he put human breast cancers in nude mice. MCF 7, which had estrogen and progesterone receptors, and BT 20 that did not. And then he treated them with either a saline injection or two injections a day of octreotide acetate. What he showed was in the MCF 7 group that the ones that also had hormone receptors, that the volume of the tumor shrank and that the doubling time, the amount of time it takes a tumor to go from the size of one lesure pea to two lesure peas went down from 13 days down to 19 days. So the doubling time was slowed down. And the tumors without the hormone receptors, the volumes were no different but the doubling time was lengthened. This was a paper that was very provocative to me because this wasn't a neuroendocrine tumor paper, this was one of the first papers ever written on breast cancer. And, have you ever read something and you walk from it, and then you go – tag! There is something in that paper that I know I read that's not registering; I need to go back and reread that. And so I reread the paper. And I'd go away, and I'd come back and I'd reread the paper. And I kept knowing that there was something in this paper that I should be paying attention to, but it just wasn't registering in my brain. And, finally, after I'd read this paper about seven or eight times, there's one line, the proverbial comedian's one-liner. It said tumors treated with octreotide acetate were grossly less vascular. Meaning they had less blood vessels feeding the tumor. I sort of jumped up, ran down the street yelling Eureka, I have found it! And I finally started to put the story together that maybe, just

maybe, instead of the Sandostatin having an anti-tumor effect on the tumor cells, maybe there was another part to the story. Maybe it was stopping the blood vessels that fed the tumor. Well, so we then split our laboratory into two sort of parts. Half of our group looked at the effect of octreotide on the tumor cell and the other half of the group went and started looking at the effect of octreotide on blood vessels. And this is work done by Darryl Kurosowa, it's in an article you can get from my office called *Investigational New Drugs*. What Darryl showed was that as you give these breast cancer cells that have hormone receptors, as you expose them to Sandostatin, that the number of cells in culture go down. At least until you reach a certain dose. But then, let me tell me, this is classic, just like everything else in the world, just because something's good, it doesn't mean that more is better. Insulin. If you give yourself the right dose of insulin, you fix your diabetes. If you give yourself too much insulin, you can kill yourself. Same way with octreotide acetate, it appears. There is an optimum dose and then if you go above that optimum dose, you can start losing effect. So, on these cells which didn't have any estrogen present, these are like a post-menopausal woman, octreotide slowed down tumor growth. What if you put estrogen in this situation? Well, number one is that you got a lot more cell growth. But number two, octreotide would still block the breast cancer growth. And, again, it did it at a very, very narrow therapeutic window. More is not necessarily better. You need an adequate dose, but not too much. Well, then Darryl asked the question, and again, thank God for residents and fellows who come to lab because they don't know enough sometimes not to ask the really good questions. And he said, maybe the way this works isn't directly on the cell; maybe the octreotide is turning on or turning off something else in the breast cancer cell. And the logical thing would, does octreotide change the sensitivity of the cell to estrogen by altering estrogen or progesterone receptors. And, again, work that's published in the *Investigational New Drugs*, octreotide markedly up-regulates estrogen receptor. It's the idea that it makes breast cancers more sensitive to the effect of estrogen, and it does so a little bit to the receptor called the progesterone receptor. Estrogen does the same thing and if you put estrogen and octreotide together, you lose this unusual effect. So it looks like, if you could get rid of estrogen and use octreotide, there might be some kind of synergistic interplay between estrogen lack and octreotide. Well, how do we block estrogen's effect? There are whole compounds, groups of compounds now, called anti-estrogens or estrogen receptor antagonists. The biggest one you may have heard of is a drug called Tamoxifen. So the question was, if we use Tamoxifen and octreotide together, would that be a good thing. And what we did is again looked at the MCF 7 cells, used octreotide, used Tamoxifen, and used them together, they were more effective than either of the two drugs by themselves. About the same time a guy named Whetbecker from Novartis in Basel, Switzerland, decided that he'd do some experiments like this but use animals instead. And he implanted these animals with breast cancers, and then he either did nothing or he treated the animals for six weeks with either Tamoxifen, the red line, octreotide or their combination. And at the end of six weeks stopped their therapy and then watched what happened to the tumor afterwards. And these the number of tumors per animal. And you can see that, if you use octreotide and Tamoxifen together, you can block the development of tumors. And that effect, even after you stop treatment, goes on for awhile and then all of a sudden the animal starts developing tumors. This is again the number of tumors. What about the size of the tumors that do develop? And, again, the combination of octreotide and Tamoxifen when you stop therapy, there's this golden window when nothing

happens and then all of a sudden, boom! it takes off again. Could it be that octreotide or Tamoxifen blocked blood vessel growth and when you stop treatment, it takes this long from there to there for the tumor to regrow a new blood supply? Well, if that's the case, the other way we can get rid of estrogen is take out your ovaries. And so what he did was waited until the mice had big tumors and in the yellow group he took out their ovaries, the red group he took out their ovaries and put them on octreotide. And here's what's really interesting. Again, this is the number of tumors per critter and what you see is oophorectomy and oophorectomy plus octreotide, the response rate during treatment was very similar. But when he stopped treatment, and the oophorectomy tumors alone regrew, and now he stopped the octreotide treatments, look how long this window before regrowth is. This is again number. If you look at the size of the tumor, it's even more impressive. Oophorectomy alone, taking out your ovaries alone, you got your response, but then after treatment, boom, they went right back up, whereas those just treated for six weeks with octreotide went for a very, very long period of time without evidence of tumor getting larger.

Well, we've showed you that the Somatostatin and analogues can directly inhibit cell growth and we've talked about what is a topic known as angiogenesis. If there is a hot topic in medicine today, it's angiogenesis. The idea that tumors require a blood supply to grow. Tumors have to gain access to the vascular blood supply to move from the gut or wherever it developed to the liver, the lung, the bone, the brain or wherever it's going. So angiogenesis not only controls tumor growth, but it controls the tumor's access to other parts of your body. But is there any evidence that Somatostatin and analogues can block blood vessel growth? Well, angiogenesis, or new blood vessel growth, is absolutely essential for an embryo to grow into a normal human being. We also use angiogenesis to repair surgical wounds or any kind of wounds. The three major forms of blindness, one of which is diabetic retinopathy, is caused by angiogenesis. Rheumatoid arthritis, what destroys your joint, is overgrowth blood vessels. Even things like psoriasis are dependent on new blood vessel growth for their development. And then, finally, cancer. Dr. Judah Folkman, who is the father of all the concepts that you're hearing today, said in the mid-1950's that if a tumor can't generate a new blood supply, the maximum size it can ever get is two millimeters. Two millimeters is about a tenth of an inch in diameter. So you never know you had it. Now, why is angiogenesis an interesting target? Well, let me tell you what this whole slide says. It says that cancer cells are really smart. Cancer cells are smarter than the entire intellect of everybody in this room combined. Every cancer cell that I've ever met has figured out a way to get around every therapy that we've ever figured out. It's called drug resistance. Cancer cells and bacterias have figured out the way to get around all kinds of evil toxic drugs. You make adriamyacin; cancer cell figures out how to get around adriamyacin. If you figure out Cis-platinum. VP 16. Tumor cells develop drug resistance. On the other hand, if cancer cells are Albert Einsteins, blood vessels are dumb as a bag of rocks. They never learn. They never can develop drug resistance. They are very slow growing, but all the things that happen to cancer cells like moving from one type to a what's called phenotype, doesn't happen with endothelial cells. And so, they're also readily accessible to anything you put in one blood vessel ultimately ends up in every blood vessel in your body. Well, the first thing that we set out to do when we asked the question, will Somatostatin and analogues inhibit blood vessel growth, is to take the cells that make up the blood vessel in culture and expose them to various concentrations of the Somatostatin and analogue

octreotide. And, as you can see, remember I said more is not necessarily better, you again have this very narrow therapeutic window where the Somatostatin and analogue concentration is most effective. If you use less than that concentration or more than that concentration, you'll lose your effect. If you put this Somatostatin and analogue on these cells, the effect starts to take place at 24 hours, peaks at 48, starts going away at 72, and is gone by 96. That's with a single exposure. What you have to do then is time your exposure so that you peak, give a new dose here, and so as you are starting to peak, you're getting a new dose, so that as this dose is going away the new dose is starting to come back up. This is work done, and the last slide was done on pig coronary artery, heart artery cells, and it was Dan Burley from Mallinckrodt was the person who got us these cells. This is work done by Roberto Dinizi out of Italy. And Dr. Dinizi showed that Sandostatin or octreotide would inhibit blood vessel cell growth, but in this case he used human umbilical vein, so when they delivered a placenta and they were going to throw away the vein that fed the placenta, they got cells out of that vein and grew them in culture. These are called huvex or human umbilical vein endophilial cells. And, again, as he added octreotide, he had a peak effect in this same range at 10 to the minus 8, 10 to the minus 9 molar, and more was not better. So, again, that very funny curve that says you better know your octreotide level or you may be getting too little or too much.

Well, all this stuff that you have just seen is in cell culture. Which is about as artificial a system as you can ever have. Cells talk to one another. Cells communicate with one another. Cells like, like people, like to be in groups. They are what are called contact inhibition. If you take cells and you have one cell over here and one cell over here like you do in culture, they can't talk and they can't interact normally. So what we wanted was a system that would be an intact living animal. And so I knew nothing about angiogenesis. So I pick up the phone and I call the father of angiogenesis, Dr. Judah Folkman, who believe it or not also is a surgeon at Harvard, at the Children's Hospital. And I say, Dr. Folkman, I am a dumb surgeon, I don't know anything about angiogenesis but I got an interesting idea I'd like to try. How could I do it? And he said, "it's very simple. This is even something a high school student could do." I said, "Well, maybe I have a chance then." And the idea is, you take a fertilized chicken egg, straight from the farm, you wash it off, you put it in an incubator, you let it sit till it's three days old. On three days old you sort of look at 'em and you can actually sort of tell which ones are going to make it and not many times. But by day six in the incubator you crack them and put them in a saran wrap hammock so that the whole egg with the fertilized embryo is sitting there and you put that whole piece of saran wrap in a piece of PVC pipe that you've cut off about that tall, so that it's sitting there, and you can look right through the open end of the pipe. On day six you can put little disk containing drugs on the chicken egg and on day seven you can see what happens. You just wash the egg, on day three put it in the incubator, crack it on day six, there it is in a piece of saran wrap, and there's a fertilized embryo in there. On day six you can see the embryo is developing, this is sitting in its piece of PCV pipe, and the microscope will look straight down through the chicken egg. This is what chicken egg's blood vessels look like. Now, they're not black. And the reason they're black is because a woman who worked in my lab who is now a plastic surgeon in St. Louis named Tina Yura, injected India ink into the heart of these chicken eggs just before we sacrificed them. This is a primary blood vessel, a secondary blood vessel, these are called tertiary blood vessels, and the little gray stuff back in here are called quatronary vessels. This is the test drug, in this case this is nothing except this is made out of metal cellulose. But the nice part is you can

see right through it and see what's going on. Now this is normal, okay. Sort of picture that in your mind. Tumors make substances called growth factors. Those growth factors are, as Larry said, the gasoline thrown on the fire. They're what make things grow. They're what make blood vessels grow. One of those things is called vascular endothelial growth factor, or VEG F. If you add VEG F to this disk, unfortunately it turns cloudy. But it also changes the way it looks. Notice now, this is called wagon wheeling. And all the blood vessels are growing towards the chemical messenger that says start to grow. What if I put in here instead of something that said grow, what if I put in Somatostatin and analogues that said stop growing. The answer is you get a big hole. Notice that the primary blood vessel is still intact, the secondary vessels are intact, but you lose tertiary and quatronary vessels. That's sort of important. Because if I gave you an angiogenesis inhibiter and knocked off the primary blood vessels, all the blood vessels in your body would fall apart and you'd die. It turns out that primary and secondary vessels belong to the patient; tertiary and quatronary vessels, which are the hole here, belong to the tumor. So knocking out tertiary and quatronary vessels is important. Another picture. It's hard to see the disk is right down here, but you can see that all the blood vessels are gone but the primary and the secondary, these little faint things here are actually on the other side of the embryo. But we then put together a whole series of chicken eggs, believe me I don't eat omelets any more. We did 21,000 chicken eggs. A young lady in my lab named Susan Wright did about 19,000 chicken eggs herself. And again, we compared octreotide, the white line, to Dr. Andrew Shalley's compound, the Vapreotide or RC 160, and showed that as you increased the amount of Somatostatin and analogue you put in the disk, you inhibited progressively more of the blood vessel growth.

But you always want to compare this to a gold standard. Is this is relevant amount of inhibition of angiogenesis? So guess what? Back on the phone again. "Dr. Folkman, what is the best inhibiter of angiogenesis today" and this was about 10-12 years ago "known to man?" And it was a combination of two drugs—Heparin, which is used as a blood thinner, and Steroids, which, we won't go there, but are used in a whole bunch of diseases. And this is Dr. Folkman's positive control for Heparin and Steroid. And as you can see, we are right in the ballpark which, at that time, was the most potent inhibiter of angiogenesis known. Remember, I told you to remember that molecule that had one amino acid changed. That's right down here. That's the same thing as Somatostatin and analogue octreotide with one amino acid change, no effect. And this is the native Somatostatin that your body and my body makes all the time.

Well, how does this compare in the same assay to the whole bunch of drugs that we all know and love or hate. All the chemotherapy drugs—methotrex 8, vinblasting, VP16, mitazantrone, adriamyacine, vincrystine, 5FU, Cytoxin, Cis-platinum, interluken, methotrex 8, era C. These are how those drugs work in this assay, and here's octreotide acetate. Here's Dr. Folkman's heparin hydrocortisone. And here's the chemotherapy. But here's the big difference. All the chemotherapies have a boatload of toxicity. Octreotide, there has never been a lethal dose of octreotide determined in rats or in humans. Early on, when people started using octreotide, there were some terrible mistakes made because people went and read papers about Somatostatin and used octreotide at the Somatostatin dose. BIG mistake. So people now have been given hundred milligram doses of octreotide. For the people in this room, if you get two milligrams a day, you're on a pretty doggone high dose. They have been given a hundred milligrams doses with no toxicity. So here's a drug that has very good effect but what's really

important about it is, it has no toxicity. But all the stuff I've shown you either is cell culture or it's a chicken. I mean, I don't know how many chickens are sitting in this room, or how many of our spouses are chickens. But it's not human. And, if it was human, like Dr. Dinizi's work, it wasn't intact. Cells didn't talk with one another. So, there was a guy about 10 or 12 years ago who started taking blood vessels out of rats and instead of blowing them into a bizillion individual cells, he put them on a baloney slicer. And he sliced the blood vessels into rings. And those rings were then put in a clot. And that was like a blood clot without blood. It's called a fibrinthrombin clot. And he could get those rat aortic rings to grow. New blood vessels. So our lab said, damn, if you can get a rat's blood vessel to grow, why can't you get a human's blood vessel to grow? Well, there aren't many people in this room who are going to let me take a piece of their blood vessel even in a research project, so we thought and we thought and we thought, where was a source of blood vessels that were thrown in the garbage can? And the answer went back to placentas. When a woman delivers a baby, if the baby is healthy and wealthy and the placenta looks normal, it's pitched in the garbage can. So we went to our IRB, the people who guard human subjects, and we said, if the nurse would pick it up out of the garbage can and put it in a bag so we don't know what patient it came from, the patient's anonymous, and the tissue is discarded, can we use those placentas in research? And the answer was yes, we know nothing about the patient and the tissue was not needed for anything else. So what we did is, we brought the placentas back to our laboratory and, being surgeons, we dissected out the blood vessels, not out of the umbilical cord but out of the placenta itself. So now you have a tube. So what we do is we take that tube and we just run our scissors length-wise and so now we have a flat sheet of blood vessels. And then we just take a little punch, like a leather punch, and punch out two millimeter in diameter disks of real genuine certifiable blood vessel that's human. And we imbed it in the same kind of clot as Dr. Nicosia did with his rat aortas.

These are what the boys in the lab call my cheeapets. This is a human blood vessel and these are new blood vessels growing out of the cut edge of the human blood vessel. This out here is the fibrinthrombin clot. We tried a whole bunch of different things. We've tried ager, which is like jello. We've tried other things. Turns out that blood vessels need, like climbing roses, a lattice to climb on. The fibrin and the thrombin, as you are about to see, make a mesh and these blood vessels snake through that mesh and hold on like a climbing rose. Well, how do blood vessels grow? It turns out that nobody had ever grown a human blood vessel in culture before. So we started out at the beginning. And we said, how does a human blood vessel grow? Well, this is the fartherest part out into the clot. And that means it's the newest. And that says that there are endothelial cells and those endothelial cells are in basically solid cords. As these blood vessels begin to mature, they start to develop what are called lipid vacuals, our friend cholesterol, HDL, LDL, all those fats collect as lipid or fat globules interspersed in these cells. And then somehow by magic they all start to coalesce and the little septums between them all fall apart and there you go, that's the lumin or the whole in the blood vessel. And that's the most mature blood vessel. So these are real genuine human blood vessels, they have all the characteristics of blood vessels, they stain with all the appropriate stains to prove that they really are blood vessels. And they grow in culture in a very predictable fashion. If you. . . they require serum, and this is cow serum, to grow. If you don't have any cow serum, nothing grows. And over time the number of wells, if you plant a 132, 80 of them begin to grow, you lose a

couple to infection, and now they start to grow, and down here even more of them grow over time. So, the incidence of angiogenesis increases in this culture over time for about two weeks. I am going to give you a very important concept, and this is a really hot new concept. Blood vessels exist in two states. Asleep or quiescent and then they undergo what's called the angiogenic switch. Somebody, the big guy, turns the switch, and I'll show you that that's maybe in certain cases tumor induced, and the cell changes pheno type or the way it looks. It goes from sitting there doing nothing to starting to grow. It's called the angiogenic switch. That's what the incidence does. How many of these went from resting to proliferative? And you can see it goes up in a very linear fashion. Once you've gone through this switch and you begin to grow, how fast you grow is also very linear. I'm really sorry that this room is so miserable for slides but this is the vessel on day one, on day five you can see that the blood vessels are about here, on day ten they are out even farther, and by day fifteen they almost fill the well. So that the blood vessel grows in a very predictable fashion. So two things that are important. One, taking resting and making it grow; and two, effecting the rate of that growth. That's called promotion. So we have initiation and then we have promotion. Here's how the length of a blood vessel grows over time. This is day seven, day 13 to 15, and day 21. And this increase is very very linear.

Well, how does octreotide do in this? Well, first you need a control. So I'm stuck again. Guess who I call? Back on the phone to Dr. Folkman. And Dr. Folkman then says, well, here's a dose of heparin steroid, the green line that I think will work. But it didn't. It looked just like our untreated group, which is the red line. So we went up ten-fold and lo and behold, nothing happened. So we went up another ten-fold to hundred times more than Dr. Folkman had guessed, and we were able to block blood vessel growth entirely. What about octreotide acetate? Well, after day six, nothing grew at all. But why did things grow between day one and day six and then nothing new after day six? Let me tell you, a lot of late night hours and arguments over Domino's pizza and coca-cola between, occasionally something other than coke but not me, I don't like beer. Anyhow, so between day zero and six we didn't know why the drug took effect on day six but there was something happening in here. So one of the guy's in my lab said, well, gee, maybe the Somatostatin and receptors don't exist on a normal blood vessel but maybe they do on a growing blood vessel. Another one of those Eurekas, I think you've got it. And so we started asking the question, do receptors for Somatostatin exist in normal blood vessels? You saw beautiful pictures by Dr. Kvols of OctreoScans. See any blood vessels? Didn't see the aorta, you didn't see the heart, you didn't see anything. It's because the receptor's not there. But I'll show you in a minute the receptors for Somatostatin and analogues develop as a vessel begins to grow.

Well, one of the critical issues for everybody in this room is what does a blood vessel say to the tumor and what does the tumor say to the blood vessel. Because they talk back and forth. That makes good sense. Well, the first one is pretty easy. What's the tumor say to the blood vessel? It says grow. But does it affect initiation, does it affect promotion, what about the direction? Can a tumor say to a blood vessel, I want you to go down to Miami Beach and then turn around and come back. Can it say those kinds of things? So we set out to answer some of those. And the first question was pretty easy. You saw this picture before, all we did was take some breast cancer cells and other kinds of cancer cells and put it on top of our clot. And then said, will that change initiation or promotion. So, the first thing we showed was, is that it increased the number of blood vessels

that began to grow. Now, this is sort of very interesting. So the tumor sends out a chemical message to the blood vessel that says I need you to wake up and start growing. Now, the question is, will a regular blood vessel that grows, does a tumor make that blood vessel grow any faster than a plain old blood vessel that you have gotten to grow with just serum. And the answer is no. But this is very scary. One of the experiments that I'm not going to show you today is a guy named Chris Watson who is now a cancer surgeon at Fox Chase, put the tumor cells on, but he put them in a baggie called a dialysis membrane. So he could take the tumor cells out after one day, after two days, after three days, after four days, and after three days the chemical message for initiation had been sent, and taking the tumor out at day three you might as well have left it there because the message was not a reversible message. Terrifying to me as a cancer surgeon because the basic tenet of surgery is that if I take out the tumor, I've done something really good. Well, I can promise you that those tumors have been there more than three days. That says if I leave one little cancer cell there, I leave it in an environment that has been stimulated to have a bizillion blood vessels growing towards that one little cancer cell.

Well, what about the direction? Is a tumor able to (tape has momentary gap). So, this is sort of a hard slide to envision. But imagine you've got a plate. And the plate is covered with jello. And I cut three holes in the jello, like ice fishing. One of them has tumor cells, this has the blood vessel, and over here on the wall that you can't see is well that has everything in it that this one does except the cancer cells. Would the blood vessel grow towards the cancer cell, would it grow over there? You can see the blood vessels over here, but what's happening over here, and you gotcha. They all grow on one side. They grow over to the tumor, they don't grow the other way. So, the tumor can now say two things. One, start growing. Two, grow towards me. A directionality of vessel growth. But what can octreotide do in the presence of tumor. Well, this is the slide that you saw before, but with some revisions. No tumor, the control, (tape reverses, some text dropped) . . . is they got there before the octreotide are growing, and they are growing at a rate that God predetermined and that, taking the tumor out isn't going to help. So if you leave one cancer cell, even though you've got octreotide on board, doesn't help. So you would hope that there could be something that would slow down blood vessel growth. Octreotide will prevent the recruitment of new blood vessels but not the old ones.

So, what does the blood vessel say to the tumor? What's the other side of the coin? And the answer is, I don't know. But we're working on that. Same kind of model, it appears that we can take a blood vessel and put it in this system and we can actually see the tumor cells starting to grow towards a well that has a blood vessel in it but it won't grow to the control well. So there is a cross talk between blood vessels and tumor cells and they both want one another to get together. It's sort of like two teenagers, boy-girl, somehow they figure out, no matter the parents say, how to get together. Ask me, I've got 18, 17 and 16 year olds. So, you remember my cheeapets? This is the blood vessel again and here are the new blood vessels growing out into the culture. Well, remember I asked the question, could you show that arresting blood vessel didn't have Somatostatin receptors and new blood vessels did. And this is, I apologize, impossible to see, but this is the resting blood vessel and these are the cells here that are growing into the fibrin clot. This part here, as we come to find out, not all the blood vessel wakes up. The only part of the blood vessel that wakes up is the part that we traumatized by cutting right along here. The edge of the blood vessel. This is just what is called a hemotoxin and eason stain, this is to

give you sort of an idea if we had a room without light, where we are. But now Dr. Otorizio, Dr. Tom and Sue Otorizio, and a gentleman working in Sue's lab named Dr. Doug Bolster, have developed an antibody towards Somatostatin receptor sub-type 2. And almost all the stuff you're hearing me and Larry and Dr. Warner, Monica, talk about today about the actions of Somatostatin have to do with this sub-type 2 receptor. So, this antibody you can actually now do stains to show where that Somatostatin receptor is. This is our, what we call, just our control, and you can see here the antibody stain is dark and you can see right on the cut edge the development of Somatostatin receptor sub-type 2. And these are the blood vessels out in the fibrin clot and they all have Somatostatin receptor sub-type 2. This is at a low power, this is at a high power. Again, right on the cut edge, where you induced trauma or hypoxia, etc., you can see the development of Somatostatin receptor sub-type 2, and these are the blood vessels out in that fibrin clot with the expression of the Somatostatin receptor.

Well, if that's the case, you can show the receptor is a protein and you develop antibodies to proteins. But what about genes? Genes are where it's at. They're at the beginning. Remember, I told you Somatostatin went to the nucleus and bound to DNA, What DNA made out of? Genes. So, one of the things that we thought about is, now we have the blood vessel. The minute we take it out of the patient we can freeze it. And the little punches that we did will now grow. So, out of every individual in this room, I could take a piece of your normal blood vessel and your growing blood vessel and look at genes and the resting blood vessel and the proliferating blood vessel and figure out what genes changed during the angiogenic switch. And so what we did is something O.J. Simpson PCR, preliminary chain reactions, and this is the normal blood vessel. These are molecular weight markers in a gel, notice there is no band over here like there is here. No gene for Somatostatin receptor sub-type 2, but in the angiogenic blood vessel there is a gene for the Somatostatin receptor sub-type 2. So at a gene level there is a gene that is getting switched on that tells start making Somatostatin receptor sub-type 2 and that gene is expressed. It makes the Somatostatin receptor sub-type 2 protein, as we showed you with the other slide.

Well, this is the concept that Larry was talking about. OctreoScan, octreother, somatother, and there are going to be hundreds of these coming out, is Somatostatin plugs into a receptor. It is very much like a lamp. You plug the plug into the wall, the lamp comes on. Nice part about a lamp is you can put in a six watt light bulb, you can put in a sixty watt light bulb, you can put a six billion watt light bulb. A six watt light bulb we're now using with a hand-held Geiger counter called a neoprobe or gamaprobe. It's about the size of my laser pointer. And we can take it in the operating room. We give the patient radioactive Somatostatin, we let it clear the background, and now the tumor glows. But it has so little radioactivity that if I'm just a little teeny tiny bit away, my probe won't find it. Give you an example. Let's say my middle knuckle here is a tumor cell. And I come along, beep, beep, beep, beep. I know right where the tumor is. And that's called probe directed surgery. And we're doing that with Pentetreotide, we have our own product known as I125 landreotide and that's been published that you can find tumors that are so small that you can't find by any conventional way. If you go to a regular light bulb, you get an external scan. You saw beautiful pictures that Dr. Kvols showed you of OctreoScans. That's sort of the concept of the 60 watt light bulb. But if you put the sun, a six billion watt light bulb, plugged into the lamp, now when you turn it on it cooks everything in the room, and that's the idea of Somatother, octreother and all the other therapies.

So, and this is again a rip-off of Dr. Kvols' slide, with the circles, this is Octreotide, this is the linker that he

was talking about, DTPA, and this is the Indium 111 that gives off the radioactivity, and that's OctreoScan. Boy, I wish this showed. Okay. So the question would be, could you put a tumor in an animal and know that the tumor didn't have Somatostatin receptors. And we can do that. We can now stain them, we can do binding experiments with radioactivity, and we can look for the genes. So we picked a cell line that doesn't have Somatostatin receptors. And we implanted those cells on the butt of a mouse and then we injected the mouse with radioactive Somatostatin analogue that looked for sub-type 2 receptors. And, believe me, this blank screen here, this is a mouse right here. And this mouse is laying down belly down on a piece of photographic film, and right here is his liver. And this dark spot that you can't see here is his liver, how much radioactivity is his liver. This is a living, breathing, genuine mouse and what we do is we cut the thumb, end of the thumb of a rubber out, put a piece of cheese there, and get him to run into the thumb of the glove, and sort of get trapped. So now we can turn him over on his back so he's now laying with his little feet up in the air and this is now the mouse here and this area right here that you can't see is the radioactivity going to a tumor that doesn't have a Somatostatin receptor in any of its cells. Where is the Somatostatin receptor? It's on the blood vessels that are feeding this tumor. So the cells don't have to have a Somatostatin receptor, the blood vessels can have a Somatostatin receptor. Well, if you can take radiation to a tumor and the blood vessel, you'd better know what radiation does to blood vessel growth. Remember, I showed you that Octreotide and a bunch of drugs that we've tested block initiation, block resting going to growing. So, when we asked this question, what does radiation do, you can bet that my bet was on initiation. And the answer to that question is wrong again, fat boy. No matter how much you gave, none or all the way up to 5000 centigray or rads, which is what we give to a breast cancer or a lung cancer or whatever, none of those doses changed going from resting to growing. Uh, oh. Now I'm really worried. So the bet in the lab is now, what does it do to the rate of blood vessel growth. We've never seen anything to this point that affects the rate of blood vessel growth. Remember that's what scared the holy bejeebles out of me. So, the next experiment was the rate of blood vessel growth as we gave more radiation, the blood vessels grew less and less quickly. So now we have two things. We have Somatostatin analogues over here that block the switch, and now we have radiation that slows down the blood vessel growth once the switch has happened. What would happen if you put the two concepts together, put the Somatostatin and the radiation together. Well, first thing you need to know is that we wanted to ask the effect of the Indium Pentetreotide, the OctreoScan, and these are neuroendocrine cells here. And what we saw was, is that, yes, we could get internalization, but that the longer you exposed a cell to Indium Pentetreotide, the more bound to that cell and more went inside the cell. Remember, OctreoScan, everybody in the room has had one, you come in, they inject it in your arm, they pat you on the head, they scan you a few hours later, and come back tomorrow. What if you infused that, continuously exposed a cell to Somatostatin analogues. You would progressively increase the amount of radioactivity you could put inside of a cell. Remember, Dr. Kvols said that the radioactivity went to the garbage disposer, the lysesone. Well, this is to show you a different, maybe, perspective of this. Here we take cells, we expose them for various times, this is Indium Pentetreotide, OctreoScan, for various periods of time, and then we blow the cell apart and put it on a, what's called a density gradient. The heavy things go to the bottom, light things stay on the top. Needless to say, not to bore you, look for the peaks over here and the peaks over here. This is the plasma

membrane, the plastic of a beach ball. This is the inside, the brains, the nucleus, over here. At one hour you see it starting to bind to the membrane. By four hours you are starting to get message over here in the nucleus, and by 24 hours all of it is there at the nucleus. That's how it's controlling gene expression, that's how, and I'll show you in a minute, can control the genes for things other than itself. And, yes, you can block this, if you add plain old Octreotide Sandostatin and you then give OctreoScan when you add the Octreotide, nothing happens. And this is why we try to get people off of their Octreotide before doing their scans or their therapies. But, sort of being a surgeon, I believe that nothing happens just willy nilly. You wouldn't take a peptide to a nucleus just so it could have a vacation in the nucleus. It has to do something. So, when it goes into the nucleus, it makes sense that it would go to DNA. The red line is just the Indium Pentetreotide. The yellow line is Indium Pentetreotide plus octreotide. And the green line is what's called specific binding to the DNA of IMR 32 cells over time. This is one day. Remember, it took a day to get to the nucleus. But it's not really in the DNA yet. It takes another day to get to the DNA. If you take cells, notice the counts here are about 1000 up here, if you take cells without the receptor, what happens? And the answer is, look, the green line, 50 counts. So, basically, nothing. Comparing it another way, these are the receptor positive cells, these are receptor negative cells, and the boys in my lab who always hold your feet to the fire and they say it's not binding to a gene, Gene, it's binding to things called istones, it's just binding to the protein. So, if you throw detergent on it or you throw a protein destroying enzyme called proteays on it, you'll just wash it right off. Well, the answer is, for once in my life, I was right and you can't wash it off. It's very, very sticky and binding to that sequence of DNA.

Now, could you in the human blood vessel model, show that the Indium Pentetreotide could kill blood vessels? Well, first thing you learn is, again, every time you set out to learn something, you learn a couple of things. And here's the percent initiation in our control group that just has serum. Here's our group with Indium Pentetreotide, much nice blocking of initiation, but interestingly enough, here was Indium Chloride by itself. This is the radioactive thing, not hooked to Somatostatin, and it appears that even if the Indium doesn't get inside the cell, it can have an effect on growing blood vessels. If you look at the growth rate in millimeters per day, Indium Pentetreotide is different than the control, but even Indium Chloride will have an effect on the growth rate. And if you look at the total vessel area, which is done by something called digital image analysis that looks and draws a line around that whole thing, Pentetreotide is very effective at controlling the angiogenic response. But even the gamma rays given off by Indium, in addition to the ogeays, have a cytotoxic effect. It may be why, the argument for using Indium Pentetreotide as a therapeutic and the higher energy beta Octreother is that the Octreother can kill an innocent bystander cell, a cell that might not have the receptor. That's both the good news and the bad news. The innocent bystander might be another cancer cell that doesn't have the receptor, it might be a spinal cord cell, it might be a kidney cell, it might be any good cell as well. So there's no free lunch. When you increase the potency of the radiation's effect, you also have the potential for doing damage. Whereas, the ogeay electron that only works withinside the cell, the good news, it doesn't kill anything outside that receptor-bearing cell. But, one of your tumor cells doesn't have the receptor, it also doesn't kill it. But this is the first time in these experiments where we're seeing that the gamma energy from Indium might buy you a little bit of innocent bystander effect, although not nearly as much as Dr. Kvols' betas.

Now, something that our lab is just now starting to work on, and this has relevance to how we give octreotide normally, Sandostatin in the old days, three shots a day versus the LAR. In the old days, a year ago, two years ago in our laboratory, we thought that binding to one of these neuroendocrine tumor cells was dependent on two things—temperature. If you chilled the cells down to four degrees, the stuff would bind to the receptor on the surface of the cell but it wouldn't go inside. Because you would shut down the machinery of the cell. We knew that it was concentration-dependent. The more radioactivity, the more drug you give to the cell, the more binds. But we hadn't put into the equation is the time factor. So what we did is design this series of experiments where we varied two things—we varied the time and we varied the concentration. The question was, if you gave a little bit of drug all the time for a very long period of time, was it the same as giving a boatload of drug for a short period of time. Concept: back to basic math. Drug concentration times time might be what, remember, boy this is a long time ago, a constant. In other words, a little bit of drug for a long time is the same as a boatload of drug for a little bit of time. So, if you had hundreds of hours, you could use a little bit of drug for a hundred of hours or you could use hundreds of drugs for just one hour. So, what we did, and again it doesn't show up very well, is down here are the product, what are called milicuri hours. Goes from 190 milicuri hours all the way up to 12,000 milicuri hours. And over here is the number of cells killed. And so what we did was, we varied things going from, like 32 microcuris for as low as six hours all the way up to 512 milicuris, a big radiation dose, for three hours. And what you see is, while there's some variability in each group, the white line represents the mean. And what you see is, is there is a very linear function here that says that cell kill is a product of the amount of milicuris that you have exposing that cell's surface times the number of hours that it is exposed. So that when we are now doing some of our high dose radio labeled Somatostatin analogue therapy, we're looking at can you infuse that to keep your blood levels very very constant over time and be able to use less drug, or make the drug more effective, than had you given that same dose by just a bolus injection and the body clears it very rapidly.

Finally, I don't know, Bill, could we tilt the projector? You've seen this slide at another forum before and this is Dr. Kvols' slide with the 5FU and the streptozotocin and the streptozotocin cytoxin, and this is Dr. Kvols' with the octreotide acetate in patients with carcinoid. Dr. Lowell Anthony, Dr. Kevin McCarthy, Mr. Greg Espanan and myself have now done 30-some patients with high dose Indium Pentetreotide therapy and these patients, like Dr. Kvols had alluded to, were part of a pilot or phase one trial. These patients, the FDA required us to take patients who had failed all conventional therapy. They had failed octreotide acetate therapy, many of them had failed chemotherapy, many of them had had bones or whatever radiated, etc. And they had to have, by an outside physician's assessment, less than six months to live. And you see the light blue line is the survival of our patients treated with at least 280 milicuri doses or about 60 times a scanning dose, twice. And our median survival is about 18 months. While it's not as good as Dr. Kvols' line with octreotide, remember our line really starts where his line leaves off. So, these are people that we thought would live around six months that are averaging about 18 months of survival at a dose of 180. We have now increased our dose to 360 and then we've increased our dose to 540 milicuris. The good news is, is that none of these people have experienced any significant toxicity. No hair loss, no nausea, no vomiting, no diarrhea, none of the associated things that you

would see with high dose chemotherapy and the other good news is we've seen nobody, and we've now given over in the world, Dr. Kretting has given over four curis, we have given over three curis of activity with no effect on the kidney, which is the big worry with the higher dose betas. So acutely or chronically, no toxicity and very nice survival data in this group of heavily pre-treated patients.

Well, I'm going to leave you with one last very quick series of thoughts, and that is on growth factors. We talked about them. Growth factors are one of the critical elements for tumor growth and this is the chicken/egg model, and the growth factor we were looking for is called epithelial growth factor or EGF. And this is work done by Jan Hess of the Children's Hospital in Seattle in cooperation with our lab. This is the disk that contained no octreotide. When you increased it to 25 micrograms per disk, the EGF level markedly decreased and when you went to 50 micrograms a disk, there was nothing. Although these eggs were still alive and the amount of protein in these disks measured to be the same as all these. What's incredible, and this I might as well not show, is this line which basically is a control octreotide estrogen or octreotide plus estrogen in a group of breast cancer cells. This is the marker for a what's called a housekeeping gene. And what you can't see here is that there is an EGF message here, there is no EGF message here, there is an EGF message here, and one here for the gene level. So octreotide can also control other genes other than Somatostatin receptors in these cells.

Thank you very much. I look forward to talking to you all in the future. As you know, anybody can call me any old time.

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

August 5, 1996

Dr. Peter Schuster
Skallgasse 20
A-3403 Klosterneuberg
Austria

Dear Dr. Schuster:

I enjoyed being able to chat with you last month and hope that you had a really good time in Ireland.

You asked me for a number of reviews of my autobiography, and some of these are enclosed.

I very much appreciate your efforts with Bölau, but I am rather pessimistic that there is a market for my autobiography in German.

The September issue of *Chemistry in Britain* will have an article on Loschmidt and Couper, and of course, I will send you a copy when it appears.

Best wishes, as always,

AB/cw

Enclosures

Dr. Peter Schuster
Skallgasse 20
A-3403 Klosterneuburg
Tel: (02243) 86 484 oder 85 009
Fax: (02243) 85 019

An
Herrn Dr. Peter Rauch
Böhlau Verlag GesmbH & Co. KG
Sachsenplatz 4-6
A-1201 Wien

Klosterneuburg, den 18.6.96

Lieber Herr Dr. Rauch,

A

in der Beilage erhalten Sie eine Rezension, die gerade in der renommierten Zeitschrift "Angewandte Chemie" über das Buch von Bader erschienen ist. Sie gibt eine gute Inhaltsangabe und schürt damit vielleicht Ihr Interesse.

Ihre Idee, Dr. Baders Buch u.U. in einer Reihe fortzuführen, kann ich nur unterstützen. Auch in der Naturwissenschaft gibt es noch "würdige" Namen, wie z.B. Weißkopf oder Perutz, die beide am Leben sind. Weißkopf selbst hat eine Biographie herausgebracht. ich sende Ihnen auch dazu eine Rezension. Dies soll Ihnen zeigen, daß durchaus ein Markt für derartige "Erinnerungen" vorhanden ist.

Sehr herzlich

Ich habe Dr. Rauch auch eine Rezension Ihres Buches geschickt und gebe Ihnen auch gern eine Kopie meines Schreibens

Ihr Peter Schuster

Dr. Peter Schuster
Skallgasse 20
A-3400 Klosterneuburg
Tel: (02243) 86 484
Fax: (02243) 85 019

Klosterneuburg, den 5.7.96

Lieber Herr Dr. Bader,

ich hatte ein sehr ausführliches Gespräch mit Dr. Rauch und Frau Dr. Weiß vom Böhlau Verlag, die ich beide kenne und schätze, und freue mich, daß ich auf meinen Vorschlag prompt ein zustimmendes Antwortschreiben erhalten habe. Eine Kopie dieses Schreibens liegt meinem Brief bei.

Herr Dr. Rauch leitet den Verlag, Frau Dr. Weiß ist verantwortlich für das Programm. Der Verlag gehört jetzt zum Springer-Verlag und hat damit in Deutschland die Vertriebswege zur Hand, die das Buch seiner Bedeutung entsprechend bekannt machen können.

Was mir Sorgen bereitet ist der Druckkostenzuschuß, der leider in Österreich bei Verlagen üblich ist, zur Zeit aber nicht durch öffentliche Gelder finanziert werden kann. Die Übersetzungskosten sind sicher dabei der große Brocken. Mir wäre aber sehr daran gelegen, daß Ihr Buch auch wirklich in deutscher Sprache, und zwar in Österreich, herausgebracht wird.

Ein gangbarer Weg wäre sicher, Sponsoren zu finden, die sich verpflichten, eine bestimmte Zahl von Exemplaren abzunehmen.

Bitte teilen Sie mir Ihre Gedanken dazu mit. Sie können natürlich auch selbst mit Frau Dr. Weiß Kontakt aufnehmen. Die Frage Lizenzgebühr müßte auch noch geklärt werden.

Lieber Herr Dr. Bader, ich bin mit "Frau und Kind" von 10. 7. bis 3.8. in Irland in unserem Sommerhaus, das bald mein Schriftstellerdomizil werden wird. Unsere Adresse dort ist: Meenacarn, Lettermacaward, P.O. Donegal Town, Co. Donegal, Tel: 075-44269. Vom 20.7. bis 23.7. werde ich aber in Wien sein. Sie können mir also nach Meenacarn oder nach Klosterneuburg schreiben.

Ich wünsche Ihnen und Ihrer Frau noch viele erholsame Tage in Bexhill.

Sehr herzlich

Ihr Peter Schuster

00
~~010~~350

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

August 9, 1995

Mr. Robert Manor
The St. Louis Post-Dispatch
900 North Tucker Blvd.
St. Louis, MO 63101

Dear Mr. Manor:

I was in Europe when your very interesting article about Sigma being fined $480,000 appeared in your paper on July 10th.

This is an enormous fine and was probably so large because some five or six years ago, Sigma-Germany was accused of selling the same toxins to Iraq.

With all good wishes, I remain,

Yours sincerely,

AB/cw

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

February 16, 1996

Mr. Warren Stockwood
4 Anis Rd.
Belmont, MA 02178

Dear Warren:

It has indeed been a long time since I saw you last, as described on page 185 of the enclosed book.

Warren, don't even think of paying me. However, I would like to ask you for a favor: A number of friends in Cambridge have told me that they have found it difficult to acquire the book. It is being distributed in the United States by Trafalgar Square Publishing, at Howe Hill Road, North Pomfret, VT 05053, and anyone wanting the book need only go into any bookstore, give the store the ISBN number, 0-297-83461-4, and tell the store that the book is available for $25.00 from Trafalgar Square. Please do tell our mutual friends who might chat with you about this how to acquire the book.

With fond regards from house to house, I remain,

Yours sincerely,

AB/cw

Enclosure

February 10, 1996

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

Dear Alfred,

I know that this letter is going to come as a surprise because we haven't corresponded for some time, but this is Warren Stockwood writing to you after a long lapse. Where does the time go? It's been five years now since I retired from the Chem Lab at Harvard and it just doesn't seem possible.

A few nights ago I received a call from a Bill Merrick who used to work for the central purchasing office at Harvard and with whom I had a very nice relationship. He left Harvard and after having worked for a couple of companies, went to work for Ace Glass Company of New Jersey. One of his customers is a gentleman by the name of Phil Pivawer of the Carbo Lab in Connecticut. Phil told Bill about a book that you had written and since he knew that Bill had had a Harvard relationship , let him borrow a copy to read. When Bill read about me he called and told me about it. We also had a chance to do some reminiscing about some of the people we both knew at Harvard.

Al, I would love to get a copy of your book "Adventures of a Chemnist Collector" and would very much appreciate your autographing it for me. I'm sure it will bring back memories. Naturally I would like to pay you for it, so if you would let me know the cost, I will send a check immediately.

Please give my regards to your wonderful wife Isabel. It was always a double pleasure to see both you on your visits to Cambridge. Also let me know what you have been doing and how you both have been.

Sincerely,

Warren Stockwood

Warren Stockwood
4 Anis R.d. Belmont, Ma. 02178

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

February 28, 1996

Mr. Warren Stockwood
4 Anis Rd.
Belmont, MA 02178

Dear Warren:

Your so-enjoyable letter of February 23rd arrived the same day as a book review by Dudley Herschbach. When next you are at harvard Square, you might like to show this review to the book-buyer at the Co-op.

Many thanks for all your help and best regards from house to house,

AB/cw

Enclosure

February 23 1996

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202

Dear Alfred,

It was so very nice of you to send me your book with the kind autograph. Believe me it will be something that I will cherish and it was so nice of you to send it as a gift!!

Alfred, yesterday, I called the Chemistry Department Administrative Assistant, a girl by the name of Carol Gonzaga, who incidently remembers you, and told her about your book and how the department as well as so many faculty members were mentioned and that they would probably want copies. She agreed and I gave her the ISBN number to use.

After talking with her I called the Harvard Coop and spoke to the book buyer and told him about your book and its tie in with Harvard Chemistry and that I had talked to the department and that orders probably would come in. He was very interested and I gave him the publishing company name plus the ISBN number. I hope that this will generate some business!!

Again, many thanks and the best to you and Isabel.

Sincerely,

Warren

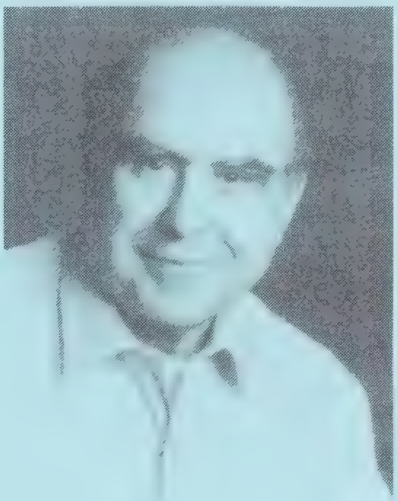
Warren Stockwood

THE SAN DIEGO CHEMIST

AMERICAN CHEMICAL SOCIETY
VOLUME 8, NUMBER 3
SAN DIEGO SECTION
APRIL 1996

"THE HISTORY OF THE ALDRICH CHEMICAL COMPANY"

DR. ALFRED BADER



STUDENT AFFILIATES OF THE ACS AT SDSU (SAACS) BANQUET AND EXHIBITS

DATE: THURSDAY, APRIL 25, 1996

Time: 5:30 PM - Social & Exhibits, 6:30 PM - Buffet Dinner, 7:30 PM - Awards, 8:15 PM - Lecture.

Price: The dinner price is $25, students with ID $15, payable at the door. *Make checks payable to SAACS.*

Book Signing: There will be a book signing of his autobiography, *Alfred Bader: Adventures of a Chemist Collector*, from 5:30 to 6:30 PM. The book will also be on sale for $25. If you plan on buying the book at the meeting, please reserve one by leaving a message at 687-5570.

Exhibits: Posters displaying undergraduate and graduate research, information from local university chemistry departments, ACS information table, and more.

Awards: 1996 Outstanding High School Chemistry Teacher Award, and many student awards.

Reservations: Must be made by Saturday, April 20. Please call 687-5570, leaving your name, phone number and number of dinners. The Section pays for "No Shows." If you reserve, then cannot attend, please cancel by April 20.

Place: Al Bahr Auditorium, 5440 Kearny Mesa Road. From 163 exit at Clairemont Mesa Blvd. (West). Make an immediate right (north) onto Kearny Mesa Road. Turn left into the Hampton Inn parking lot. The Al Bahr is behind the Hampton Inn. Free parking. (Thomas Bros. 1229-C7).

ABOUT THE LECTURE - In 1951, Alfred Bader and an attorney friend decided to start up a company to make and sell research chemicals, which they operated in the evenings and on weekends in a garage. The partners tossed a coin for the privilege of naming the new company, and Bader lost the toss. His partner was engaged to "a charming girl," Betty Aldrich, and so named the company after her - Aldrich Chemical Co.

By the mid-1960s, with Aldrich's sales at more than $2 million and its stock being traded publicly, Bader realized that even greater growth in chemical research lay in biochemistry. So he began pursing a merger with a biochemical producer, the ablest and most interesting of which, Bader says, was Sigma Chemical of St. Louis. Sigma initially rebuffed a merger proposal, but it finally agreed in 1975. With a greatly enhanced catalog of chemicals, and with an emphasis on fast filling of orders and high-purity compounds, Sigma-Aldrich grew to one of the world's preeminent suppliers of custom chemicals and fine organics and inorganics. Its sales in 1995 totaled $960 million.

ABOUT THE SPEAKER - Alfred Bader was born in Vienna in 1924. After moving to England in 1938, and Canada in 1940, he graduated from Queen's University in Kingston, Ontario in Engineering Chemistry in 1945, and from Harvard in Chemistry in 1950 (Ph.D. with Louis Fieser). Between his university studies, he worked for a Canadian paint company which was acquired by Pittsburgh Plate Glass (PPG), which offered him a position in its research laboratories in Milwaukee in 1950. In 1951, he founded Aldrich Chemical Company, which merged with Sigma Chemical Company of St. Louis in 1975. After serving Sigma-Aldrich as president and CEO and then as chairman and chairman emeritus, he started an art gallery in the Astor Hotel in Milwaukee in 1992.

Dr. Bader was the curator of "The Bible through Dutch Eyes" exhibition at the Milwaukee Art Center in 1976, and with Isabel, his wife, curator of "The Detective's Eye" exhibition in 1989. He has published widely on chemistry, art and the Bible.

Message From the Chair ~

For those of you that missed our March meeting, you missed a special evening of education and enjoyment. Professor Nagyvary presented a splendid lecture on the science of violin making. If you would like to read about what you missed, see "Modern Science and the Classical Violin - A View from Academia" in The Chemical Intelligencer, 1996, **2**(1), 24-31. What you can't replace from the evening was the performance of Zina Schiff, a concert violinist from the Bay Area that Professor Nagyvary invited. Zina played two of Professor Nagyvary's hand-crafted violins against her own Stradivarius violin. Whether your ear could tell the difference in violins or not, the music was superb! This months meeting should also prove to be of entertainment and interest. Dr. Bader is an gregarious individual and the Aldrich Chemical Company is a major success story in chemistry. I highly recommend your attendance.

There is always the time when we could use your support. This month I call your attention to the request of the education committee and the letter from ACS National in support of federal funding. These two requests would take very little of your time and would be greatly appreciated. In a request of greater time demand, I call your attention to the insert page, which is a local section survey We need to be regularly addressing whether or not we are meeting your objectives. Please read, fill out and return the enclosed survey. To show our gratitude we will be extending a $3.00 discount to the 50 yr. member meeting in June for all who return the survey and attend the meeting/lunch.

We need volunteers to organize an employment committee to assist members in the area. We would like to create a venue, most likely in the newsletter, for employers to reach members of the society with their vacancies. we are looking into establishing a web site. Can you participate in these endeavors? What other programs could be of use to you? Please read and answer the enclosed survey.

Outstanding High School Chemistry Teacher Award

The Education Committee is pleased to announce the co-recipients of the 1996 Outstanding High School Chemistry Teacher Award: Ms. Victoria Coordt of Torrey pines High School and Mr. Mike Sixtus of Mar Vista High School.

Ms Coordt received her B.A. degree in mathematics (chemistry minor) from the University of California at Berkeley and earned her teaching credential in the Graduate Intern Program there. She has taught both math and chemistry in the San Dieguito District since 1975. Since 1991, Ms. Coordt has been responsible for the Advanced Placement and Honors Chemistry program at Torrey Pines High School which produces some of the top chemistry students in the county. She also serves as coach of the Academic Team. Ms. Coordt has been very active for a number of years with local and state-wide science fairs.

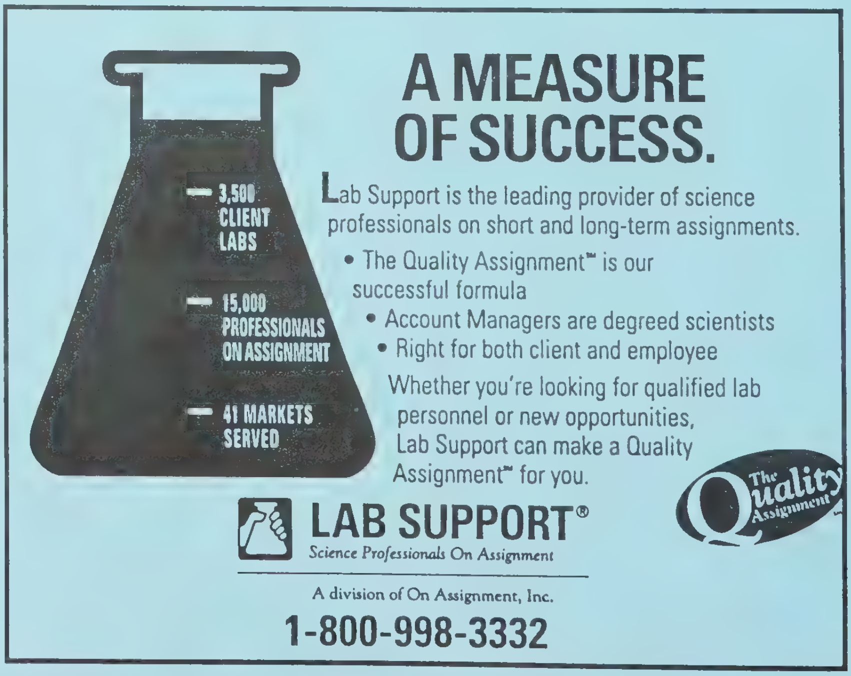
Mr. Sixtus received his B.S. degree in biology (chemistry and Spanish minors) at he University of Santa Clara and a M.S. degree in Marine Biology from San Diego State University. He holds credentials (with bilingual emphasis in Spanish) in Life Science and Physical Science. Mr. Sixtus has taught science at Mar Vista High School since 19888. He has been extremely active in high school science curriculum development at both the local and national level. Mr. Sixtus has made outstanding contributions towards this end at Mar Vista through the successful implementation of ChemCom (Chemistry n the Community) which focuses on science literacy for minority students.

The awards (plaques and $200 each for Ms. Coordt and Mr. Sixtus; $200 each for Torrey Pines and Mar Vista High Schools) will be presented at the annual SAACS Banquet on April 25, 1966.

!! PROCTORS NEEDED !!

1996 High School Chemistry Competition
Date: Saturday, May 18, 1996
Time: 10:00 am - 1:00 pm
Place: University of San Diego
(Camino Hall)

There is a new exam format this year. We need your participation to make it a success! For more information, please call Tammy Dwyer at 260-4030.



1996 ACS MEMBER SURVEY

SAN DIEGO SECTION

As your Local Section, we want to serve you and provide activities that you will find useful and interesting. The only way that this can happen is for us to hear from you about what you want. Please take a minute to fill out this survey. We will use the results to plan the programs that you want to see. Thanks.

Name: ____
Phone Number: ______________ e-mail __________
Zip Code:_____ Work__________ Home__________

1. What is your employment status? (circle one)

Academic Industry Government Consultant Retired Student Unemployed Other

2. How many ACS Local Section activities have you attended in the past 2 years? ____________
How many other professional meetings? _____ What societies? ____________

3. Rank the following meeting criteria in order of importance to you: (# 1 to 6, with # 1 being most important)

___ Topic ___ Network/Social ___ Location
___ Cost ___ Time of Meeting ___ Menu

4. Which of the following types of meetings are of interest to you:

___ Dinner Meeting and Speaker ___ Lunch Meeting with Speaker ___ Panel Discussion
___ Field Trip/Company Tour ___ Social Only (Happy Hour) ___ Short Course*
___ Workshop (GC basics, etc.) ___ Satellite TV Seminar ___ Lunch Groups**

5. Circle the FOUR topics that you would like to see featured at a meeting:

Analytical Environmental Biotechnology Chem. Education Safety Internet
Medicine History Computers Polymers Inorganic Organic
Geochemistry Oceanography Wine/Beer Making Art & Chemistry Atmospheric Drug Design
Chem. Demos Semiconductors General __________ Other __________

6. Please specify your preference for a regular meeting schedule: (please circle your choices)

Week of the month:	1st	2nd	3rd	4th	Any	
Day of the week:	Mon.	Tues.	Wed.	Thurs.	Fri.	Sat.
Meeting start time:	12:00 Noon		6:00 PM	7:00 PM		8:00 PM
Meeting frequency:	Every month		Every other month			Every Quarter
Number of weeks notice:	One week		Two weeks		Three weeks	

7. Do you read *The San Diego Chemist?* ____________
Do you have any suggestions for items that would make the newsletter more useful for you? __________
____
Do you read the Advertisements? _____ Have you used the services of the advertisers? _____

8. What Local Section committees do you think are important? (circle your choices)

Education Employment Younger Chemists Women Chemists Environmental
Public Relations Newsletter Older Chemists National Chemistry Week Biotech Expo
Student Affiliates Graduate Students

Would you be available to serve on one of these committees? _____ Which one? _______
Which committees would you like to know more about?______________________

9. How can the San Diego ACS serve you better? ______________________
____
____

10. Are you interested in serving as an Executive Board Member? ______________

11. Any other comments? ______________________________

* Short Course Information on the other side

** Lunch Groups implies 4-6 people getting together over lunch to discuss a topic of common interest e.g. combinatorial chemistry or chemistry on the internet etc.

RETURN THIS SURVEY FOR $3.00 off the June 50 year member Luncheon - Reply to:
SD Section of the ACS, P.O. Box 370852, San Diego, CA. 92137-0852

The American Chemical Society Short Courses cover virtually every area of importance to chemical scientists, including chromatography; spectroscopy; quality; computers in chemistry; environmental chemistry; organic, polymer, and physical chemistry; biological, pharmaceutical, and medicinal chemistry; and management/business.

For More Information about Short Courses or an update on newly scheduled courses, contact the ACS Educational Services/Short Course Office at (800) 227-5558 or (202) 872-4508 (phones)or (202) 872-6336 (fax). Visit the catalog on the following web site:
http://www.acs.org/edugen2/education/conted/about_sc.htm
or send an e-mail message to shortcourses@acs.org

Association for Women in Science Meeting

The San Diego chapter of the national organization, the Association for Women in Science (AWIS), is planning a reception to recognize a major milestone, the 25th Anniversary of National AWIS and the 10th Anniversary of the local chapter. AWIS is a non-profit organization dedicated to improving the educational and professional development of women in all fields of science. The reception is scheduled for Saturday, April 27th, 1996, from 6:00 to 8:00 pm at the San Diego Natural History Museum in Balboa Park. The celebration will allow local women in science the opportunity to gather, share, and reflect on the achievements of women scientists over the past 25 years facing the challenges of a technologically and socially demanding era. The evening program will include special recognition of a local woman scientist, Pamela Surko, Ph.D., who was recently presented with the honorific title of AWIS Fellow by the national organization; Dr. Surko is the one of only 25 women scientists throughout the nation to have received this honor. In addition, Council Member Christine Kehoe will present a San Diego City Proclamation in honor of the dual anniversary celebration, and past AWIS-San Diego Board Members will also be recognized for their contributions to the goals of the organization. Throughout the evening guests will have the opportunity to view many of the Museum's exhibits, including their current Main Exhibit, "Planet Insect" featuring the larger-than-life robotosized insects, listen to the soft jazz sounds of "Tobacco Road", enjoy the appetizer buffet including champagne and other beverages, and participate in a raffle for door prizes. Admission is $15 per person ($7 per person for students), both men and women are welcome, and valet parking will be available. No tickets will be sold at the door, so to register for this event or to make a donation in support of the efforts of AWIS (monetary, door prize or "in-kind" donations are always welcome and appreciated), call the AWIS-San Diego Anniversary Hotline at 619-603-2531.

ACS is sponsoring an open letter to President Clinton and the Congressional Leadership that outlines the critical need to continue a strong level of support for research and education in the chemical sciences. As members of the ACS Federal Funding Networks, you have carried the message about science to Congress many times. Now, with the possibility of support from 151,000 ACS members, science will have the visibility in the critical budgeting process that it demands. Help make history. If you simply use your e-mail, you can sign up to send your name and address, or via the fax-back forms in the March issue of ACSess. As every voice counts, we hope that you will join thousands of your colleagues in making this effort a success.

An Open Letter to the President and the Congressional Leadership

We, the undersigned concerned citizens and members of the American Chemical Society, are deeply disturbed by the decreasing level of federal support for science and technology, especially as it relates to the chemical sciences. Investment in science and technology generates significant returns for our country. Under current projections for a seven-year balanced budget, funding for federally-supported science and technology will decrease by approximately one-third. Such a large decrease in support threatens future discoveries that can help protect our citizens from disease and pollution, provide for a robust national economy, and improve the quality of our lives.

For the sake of the future of our Nation, we urge you to strengthen federal support for science and technology as part of balancing the federal budget.

Sincerely yours,

Ronald Breslow, ACS President
Paul S. Anderson, ACS President-Elect
Brian M. Rushton, ACS Immediate Past President
Joan E. Shields, Chairman, ACS Board of Directors.

SIGN UP VIA E-MAIL AT PETITION@ACS.ORG

****

To join the ACS Federal Funding Networks or for more information, send an e-mail message to the address below.
ACS Federal Funding Networks Dept. of Gov't Relations & Science Policy Office of Science & Technology Policy 1155 16th Street, NW Washington, DC 20036 202/452-2127 fax: 202/872-6206 e-mail: nsfnet@acs.org or nihnet@acs.org

The American Chemical Society, San Diego Section
1996 Summer Science Partnerships

The San Diego section of the American Chemical Society is launching a new program to provide local high school chemistry teachers an opportunity to perform research in an academic laboratory during the Summer of 1996. The award shall be used to provide a summer stipend ($3,000 for 8 weeks) for the high school teacher while working on a project in the laboratory of a research-active faculty member at a local university. *The funds may be used for salary only and may not be used for supplies, chemicals, or travel.*

PROPOSAL INFORMATION

1) The principal investigator (university faculty member) arranges a collaboration with a local high school chemistry teacher and develops a proposed research plan.
2) Five copies of the proposal are submitted to the San Diego ACS section by the principal investigator.

PROPOSAL FORMAT Applicants are required to submit proposals in the following format:

1) Cover page signed by the principal investigator and high school teacher.
2) A one page outline of objectives and methods.
3) Current curricula vitae for the principal investigator and high school teacher.
4) Current level of funding for the proposed project.

CLOSING DATE FOR PROPOSALS

Proposals must be received by the San Diego ACS section no later than **May 1, 1996**

For application, call Steve White at 550-7662. Submit the completed forms to: 1996 Summer Science Partnerships, c/o ACS San Diego Section. P.O.Box 370852, San Diego, CA 92137-0852

Alfred Bader
Aldrich Chemical Founder

4/22 4:00PM	UCSD "Josef Loschmidt, the Father of Molecular Modeling" ('JLFMM')
4/23 10:45AM	SD Museum of Art ('SDMA') "The Rembrandt Research Project and the Collector" (charge)
4/23 3:30PM	SDSU 'JLFMM'
4/23 8:00PM	'SDMA' "The Adventures of a Chemist/Collector" ('ACC')
4/24 9:30AM	Tierrasanta Lutheran Church "The Bible thru Dutch Eyes: Rembrandt and the Jews"
4/24 12:00PM	Centro de Graduados, Tijuana 'ACC'
4/25 8:00PM	Al Bahr Temple "The History of the Aldrich Chemical Company" SAACS Banquet
4/25 2:00PM	Scripps Res. Inst. "R. Anschaez, A.S. Cooper, and J. Loschmidt A Detective at Work."

For more information, contact Professor Lars Hellberg, SDSU 594-5570

San Diego Section
1996 Calendar

4/25	**SAACS Banquet** Alfred Bader *"The History of the Aldrich Chemical Company"* Al Bahr Temple
6/8	**ACS 50 Year Member Luncheon** Jack Roberts, Cal Tech. *"An Illustrative Retrospective of Organic Chemistry"*
8/25-29	**ACS National Meeting** - Orlando, FL
9/24	**September Section Meeting** - ACS Tour Speaker Glenn Crosby, Washington State University *"Making Difficult Ideas Easy: Presenting Complex Material in an Understandable Way"*
10/30-11/2	**32nd Western Regional Meeting** Cathedral Hill Hotel, San Francisco, CA Chair: Art Diaz, San Jose St.U, 408-924-3944
11/10-	**National Chemistry Week - ChemExpo** Balboa Park

EXECUTIVE BOARD - 1996
SAN DIEGO SECTION OF THE AMERICAN CHEMICAL SOCIETY

Chair Steve White, Ligand 550-7662
Chair-Elect Todd Talashek, Kelco 467-6670
Past Chair Ben Fabian, Formulabs 741-2345
Secretary John Urlaub, Formulabs 741-2345
Treasurer Frank Miskiel, Kelco 467-6685
Councilors
  Suzanne Blackburn, APCD 272-8170
  Dale Chatfield, Chemistry Solutions 458-1324
  Barbara Sawrey, UCSD 534-6479
  Shirley Welsh, Fisher Scientific 635-9155
Alternate Councilors
  Tony Bottone, Gilson, Inc. 484-6839
  Tammy Dwyer, USD 260-4030
  John Palmer, UCSD 534-5906
  Scott Shackelford, Alliance 558-4304
Members at Large
  Fred Garces, USD 260-2636
  David Wallace, Chugai 535-5922

Education Tammy Dwyer, USD 260-4030
Employment TBA
Women Chemists & Younger Chemists
  Michele Ramirez-Weinhouse, Gensia 480-2264

San Diego Chemist Newsletter
Editor TBA
Newsletter Ads Tony Bottone 484-6839

THE SAN DIEGO CHEMIST is published by the San Diego Section of the American Chemical Society on an irregular basis.

Advertisers: The current ad prices are as follows: Large (4.5"x4.75") for $150, Small (2"x3" or 4.5"x1.5") for $50. All measurements are (Wide x Tall). We cannot accept ads other than these sizes. Send your camera-ready art and payment to the mailing address. Publication deadline varies.

AMERICAN CHEMICAL SOCIETY
SAN DIEGO SECTION
P.O. BOX 370852
SAN DIEGO, CA 92137-0852

Non-Profit Org.
U.S. Postage
PAID
San Diego, CA
Permit No. 439

Dr. Alfred Bader
924 East Juneau Ave #622
Milwaukee, WI 53202

Please Do Not Delay -
Contains Dated Meeting Announcement

Alfred Bader Visit – April, 1996

Accounting of Books:
As of 4/26/96 (Noon)

32 books sold x 25.00 = $800.00
½ share, SAACS–SDSU = 400.00

½ share, Dr. Bader: 400.00
2 Checks at 25.00 each = 50.00
1 check, from SDSU SAACS = 350.00
Total: 400.00

Sale of Books at TSRI (La Jolla), PM of 4/26/96: 75– cash

Total sold San Diego
38 for $475–

Jim (o) 268 4488

Schedule of Dr. and Mrs. Alfred Bader in San Diego

Date: February 21, 1996

Date	Time	Place	Event; Related Matters
4/22	12:15 PM	Airport	Arrival via Midwest Express
4/22	4 PM	UCSD	Organic Seminar, UCSD Title: "Josef Loschmidt, The Father of Molecular Modeling"(JLFMM)
4/22	Evening	La Jolla	Dinner with Faculty, UCSD
4/23	10:45 AM	San Diego Museum of Art(SDMA)	"The Rembrandt Research Project and the Collector" (In SDMA conference room-undetermined crowd size)
4/23	3:30 PM	SDSU	Department Seminar, SDSU Title: "JLFMM"
4/23	6 PM-Drinks 7 PM-Dinner 8 PM-Lecture	SDMA	"The Adventures of a Chemist/Collector"(ACC); to the "Explorers Club" of San Diego (approx. 100 people)
4/24	9 AM	SD Luth Minsters (Tierrasanta Lutheran Ch)	"The Bible thru Dutch Eyes: Rembrandt and the Jews"
4/24	12-1 PM (bit more casual!)	Centro de Graduados, Instituto Tecnologico, Tj	Seminar: "ACC" (To Lunch afterwards, at a nice place in Tijuana)
4/24	Evening	Dinner	L. Hellberg
4/25	5:30 PM	High School Nite-ACS Mt	Talk: "The History of the Aldrich Chemical Company" (about 300 pers., at Al Bahr Temple; buffet dinner
4/26			
4/27	1:00 PM	Departure for Milwaukee	

The Probst Memorial Lecture Series celebrates its Twentieth Anniversary. Previous guests have been

1976 **Dr. Robert E. Buckles**, "Halogen Addition Reactions: Simple Reactions Which Are Not So Simple"
1977 **Dr. Paul D. Bartlett**, "Competing Reaction mechanisms in Organic Oxidation"
1978 **Dr. Melvin S. Newman**, "New chemistry Involved in Studies on Synthesis of Carcinogenic Compounds"
1979 **Dr. Carl Djerassi**, "The Future of Human Birth Control"
1980 **Dr. William N. Lipscomb**, "How Do Enzymes Work?"
1981 **Dr. Mildred Cohn**, "Nuclear Probes of Enzymatic Reactions"
1982 **Dr. Leo A. Paquette**, "The Dodecahedron Story"
1983 **Dr. Michael Kasha**, "A New Look at the History and Design of String Instruments: Guitar, Viola, Violin"
1985 **Dr. Paul Gassman**, "How to Bend a Carbon-Carbon Bond"
1986 **Dr. Jacqueline K. Barton**, "Molecular Travels Along the DNA Strand"
1987 **Dr. John William Birks**, "Nuclear Winter - Ultraviolet Spring"
1988 **Dr. Peter Kollman**, "Use of Computer Simulations in Chemistry"
1989 **Dr. Norman R. Farnsworth**, "Prospects for Finding Anticancer Drugs from Plants and Marine Organisms"
1990 **Dr. Lawrence K. Montgomery**, "Organic Superconductors? You Must Be Kidding"
1991 **Dr. James L. Dye**, "Electride Structures"
1992 Dr. Harold Kroto, "C_{60}, Buckminsterfullerene, The Celestial Sphere Which Fell to Earth"
1993 **Dr. Frederick Hawthorne**, "Boron Neutron Capture Therapy"
1994 **Dr. Terence C. Owen**, "Pretty Colored Chemistry for Biology and Medicine: Better Things for Better Living .."
1995 **Dr. Roald Hoffmann**, "The Same and Not the Same: the Rift Between the Sciences and Humanities"

Book Sale and Signings -- Dr. Bader's book *The Adventure of a Chemist Collector* will be on sale at each of the receptions following his lectures for $25.

Twentieth Annual

WILLIAM J. PROBST MEMORIAL LECTURES

DR. ALFRED BADER

Founder, Aldrich Chemical Company

The Department of Chemistry and the Chemistry Club

Sponsors: Department of Chemistry, Chem Club, Excellence in Undergraduate Education, Student Organizations, College of Arts and Sciences, Graduate School, and Student Assessment

The Rembrandt Research Project and the Collector

Tuesday, April 16
7:30 p.m.
Lovejoy Library Auditorium

With Dr. Bader's life-long interest in art and passion for 17th century Dutch paintings, the works by Rembrandt and his students have received special attention. Many paintings from this school are unsigned or the artist debated. Since 1968 a group of eminent Dutch scholars, known as the Rembrandt Research Project, have been studying paintings from this period and assigning works to the master, his students and followers. While Dutch paintings have been closely examined and physical facts published in several volumes, the conclusions and assigned artist are not always convincing.

Senior Assignment Poster Session

Wednesday, April 17th
1:00 p.m.
Maple-Dogwood Room, University Center

You are invited to view the posters and discuss the projects with students at this informal session.

History of Aldrich and Sigma-Aldrich Chemical Company

Wednesday, April 17
3:30 p.m.
Maple-Dogwood Room, University Center

Dr. Bader, co-founder of Aldrich, later Sigma-Aldrich Chemical Company, started as a displaced youth, sent from Austria to Canada during World War II. His achievements from beginning in an internment camp, studies at Queens University, Canada,, and Harvard University, and establishing a successful chemical company attest the remarkable abilities and determination of Dr. Bader. With the financial and legal support of an attorney friend, a company was founded that provides specialty chemicals largely to researchers was founded. Through interactions with chemists here and abroad, Dr. Bader established both suppliers and markets for unusual and new compounds.

The Adventures of a Chemist Collector

Wednesday, April 17
8:00 p.m.
Room 3114, Science Building

As a youth collecting stamps and drawings, Dr. Bader showed his propensity for collections. His interest has continued, with special interests in collecting and restoring 17th century Dutch paintings. Dr. Bader is well-known for his discoveries of old masters, quests that are presented in a humorous, knowledgeable, and richly illustrated seminar. The cleaning and restoring of old paintings has adventures such as the discovery of forged signatures and the overpainting of an original work.

The Bible Through Dutch Eyes

Thursday, April 18
2:00 p.m.
Maple-Dogwood Room, University Center

Many 17th century Dutch paintings depict biblical scenes, with nearly equal numbers of paintings showing stories from the Old and the New Testament. Dr. Bader's study of paintings of this period is directed to the interpretation of the scene and the biblical story depicted. His expertise in art and knowledge of the Bible lead to interesting and convincing, though sometimes controversial assignments. Paintings are presented with understanding and interpretation with a Biblical view.

Early Chemists - Richard Anschutz, Archibald Scott Couper, and Josef Loschmidt

Thursday, April 18
7:30 p.m.
Maple-Dogwood Room, University Center

History rewards discoveries that are published first, giving little recognition to those who come in second. Dr. Bader discusses his research into the writings of early chemists, which suggest that the structure of aromatic compounds, the benzene ring, was first proposed by Josef Loschmidt, a little known high school teacher. Evidence is presented that Kekule was familiar with Loschmidt's book when he presented his similar theories on the structure of benzene for which he achieved lasting fame.

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

May 1, 1996

Richard Stone, M.D.
227 East Silver Spring Drive
Milwaukee, WI 53217

Dear Richard:

Please don't mind that several long lecture tours all over the country have delayed my responding to your most interesting letter of April 8th.

The world is, indeed, between the devil and the deep blue sea as far as our attitude toward science is concerned.

On the one hand, science - and chemistry, particularly - has gotten such a bad reputation that many able youngsters don't want to consider chemistry. That is bound to slow down improvement of life.

On the other hand, we produce many chemicals, such as CFC's, which on the surface seem harmless and yet which can have such hidden dangers.

Rachel Carson's book was a turning point in our perception, and others are in the pipeline, dealing with the threats of some industrial chemicals and of genetic engineering.

Unfortunately, the examples of DuPont defending CFC's and the tobacco industry lying through its corporate teeth don't bode well.

A talk which I gave recently at Arizona State University might interest you and will surely remind you of some of my teachings when you were ten and eleven.

With all good wishes, I remain,

Yours sincerely,

AB/cw
Enclosure

RICHARD STONE M.D.
EYE PHYSICIAN AND SURGEON

TELEPHONE (414) 961-2020
227 EAST SILVER SPRING DRIVE
MILWAUKEE, WISCONSIN 53217

April 8, 1996

Alfred Bader Fine Arts
924 E. Juneau Avenue
Milwaukee, WI 53202

Dear Alfred:

I enjoyed immensely reading your book. You have truly had a wonderful, productive and philanthropic career.

Being a physician, I share many of your interests in chemistry and art. While reading through a copy of Natural History, an article caught my eye. I have enclosed it for your perusal. Certainly chemistry and all of its by products have been one of the most important factors in helping civilization. From new drugs to household items, the list is endless. However, as the enclosed article points out, chemicals are a two-edged sword.

Unfortunately, because of economics involved, I do not believe that large chemical companies are conducting or funding adequate research to discover any potential side effects of their products. This might be an area in which your expertise would be welcome. I would very much like to hear your thoughts on this subject.

Yours very truly,

Richard

RICHARD STONE, M.D.

RS/mep

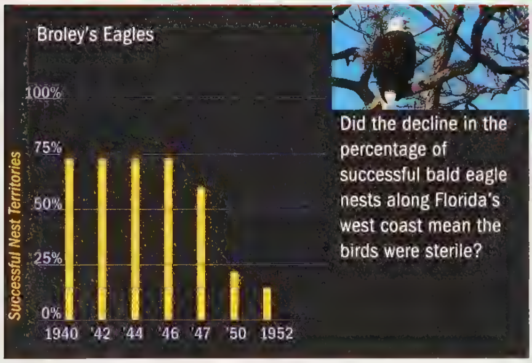
Horm
Sabo

Synthetic chemicals in the environment may be wreaking havoc with the

In July 1991, a group of scientists—including Theo Colborn, then a fellow at the W. Alton Jones Foundation, and John Peterson (Pete) Myers, the foundation's director—gathered at the Wingspread conference center near Racine, Wisconsin, to discuss their concerns about hormone-disrupting chemicals in the environment. They were disturbed by mounting evidence that synthetic compounds found in pesticides and industrial chemicals were wreaking havoc with endocrine systems.

The scientists shared information on a broad range of species with problems that ranged from thyroid dysfunction, decreased fertility, and gross birth deformities to feminization of males, masculinization of females, and compromised immune systems. Many of the chemical compounds under discussion had an affinity for estrogen receptors in particular, and their effects on wildlife paralleled those seen in humans exposed to the synthetic estrogen DES (diethylstilbestrol). Although environ-

Omens



Did the decline in the percentage of successful bald eagle nests along Florida's west coast mean the birds were sterile?

J. H. [illegible], Photo Researchers, Inc.

Hunters first noticed the dwindling number of otters in the English countryside. Conservationists believed the cause was chemical.

Toni Angermayer, Photo Researchers, Inc.

The late 1940s: Gulf Coast, Florida

Charles Broley began his study of Florida's bald eagles in 1939 at the suggestion of the National Audubon Society. In the early 1940s, Broley followed 125 active nests along the peninsula's west coast from Tampa to Fort Myers and banded some 150 young eaglets each year. In 1947 the picture suddenly changed. The number of eaglets began dropping sharply, and in the succeeding years, Broley witnessed bizarre behavior in many of the eagle pairs. At nesting sites he had visited for thirteen years, two-thirds of the adult birds appeared indifferent to nesting, courtship, and mating. As Broley continued his work through the mid-1950s, he became convinced that 80 percent of Florida's bald eagles were sterile.

The late 1950s: England

Although otters were no longer as plentiful as in earlier times, the traditional sport of otter hunting continued relatively unchanged into the mid-twentieth century. To the sounds of horns and baying hounds, hunters still pursued their prey; by the end of the 1950s, however, they began to have trouble finding otters to hunt. When conservationists finally took note of the problem, some suspected the pesticide dieldrin, but later work pointed to another synthetic chemical.

From *Our Stolen Future: How We Are Threatening Our Fertility, Intelligence, and Survival—A Scientific Detective Story,* by Theo Colborn, Dianne Dumanoski, and John Peterson Myers. Copyright © Theo Colborn, Dianne Dumanosk

Paul A. Sounders

Each foot of a dog completing the Iditarod may touch the ground 1.3 million times.

University of Alaska Fairbanks

University of Alaska Fairbanks

Top: In the past, dogs were commonly used to transport supplies, sometimes pulling sleds, sometimes serving as pack animals. Bottom: Dogs of many types make up a sled dog team in the 1908 All Alaska Sweepstakes. Facing page: At the finish of the 1994 Iditarod, a dog naps while waiting to be unhitched. The dogs live outside, so sleeping on snow is no hardship.

generations in any musher's kennel, you come up with the same dogs—Wright's and Attla's with village dogs." The village dogs came from a 100-mile stretch along the Yukon from Tanana to Galena, with spurs off to places like Huslia. On occasion, salukis and other hounds were crossed into particular lines for speed. The result was the Alaskan husky.

Like Wright, many mushers engage in close line breeding in an effort to perpetuate the good qualities of their best dogs and eliminate the uncertainty of outside bloodlines. They believe they can spot and weed out those canine genetic ailments that are recessive and often fixed along with positive traits through inbreeding. But the best mushers recognize that inbreeding is potentially dangerous and consequently look to maintain hybrid vigor—having dogs from distantly related lines, crossing in another breed such as a border collie, or obtaining an old-style native husky, which might not have much Aurora blood, from a remote village on the Bering Sea.

The pressure to produce superior dogs is intense. Sprint mushers strive to have "a whole team of super animals," Attla says. Not fully mature until two years old, sprint dogs are at their peak for about five years. Then, according to various descriptions, they burn out or wise up, meaning they begin to hold something in reserve. Wright and Attla say they used to sell their older dogs and less than exemplary sprinters to "Iditaroders" in the early years of that race, first run in 1973.

Much has changed since then. With her four victories in the late 1980s, Susan Butcher brought to the Iditarod international visibility and an emphasis on dog care, which in many quarters had been indifferent at best. With the success of his houndy huskies in 1992 and 1994, Martin Buser shifted the focus to speed and the mental attitude of the dogs.

"It used to be that geographical divisions accounted for differences between dogs," Buser says. "But now there is so much traveling and interbreeding that good breeders are following natural selection at its finest. People are breeding to their likes and dislikes." Buser wants happy, outgoing, eager dogs with good locomotion, having calculated that each foot of each dog completing the journey from Anchorage to Nome will touch the ground 1.3 million times. Also, because he believes that big dogs often end up dropped, he likes males and females of equal size, about fifty-four pounds—an idiosyncrasy not shared by other mushers. But like most successful mushers today, Buser prefers to have as many trained leaders on his team as possible, should one or more falter.

A walk through Buser's Happy Trails Kennel, nestled in a region of lakes, near the Little Susitna River, with mountains looming in the distance, reveals a range of personalities and phenotypes, from his lop ear, short-coated houndy dogs to the more traditional husky look of leaders D2 and Dave. When the time comes to run, even in front of the all-terrain vehicle used for training during August, Buser's dogs are ready and eager to log a few of their 2,000 annual miles. Buser, who knows intimately the gait, habit, and personality of each dog, issues commands in a normal tone of voice. He stops when the dogs are performing well to congratulate and pet each one. This positive reinforcement, representing a new wave among mushers, pays off.

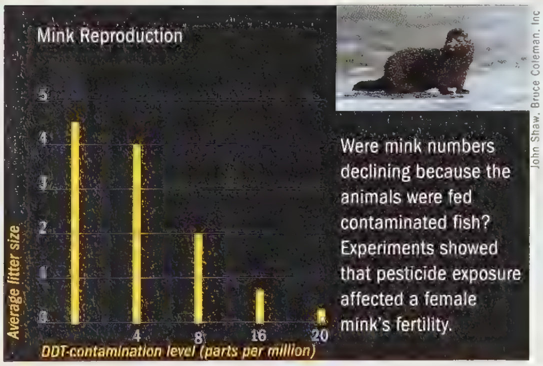
High-quality nutrition and veterinary care, good breeding and upbringing have greatly improved the health of the Alaskan husky, providing the dogs with a better life than many house pets have and certainly better than those of their forebears. Excellent Alaskan huskies are now available to almost anyone with the money to buy and maintain them. But money alone cannot purchase victory. All else being equal, the top mushers in any race will be those who share a deep, inarticulate bond with their dogs. □

onal tage

endocrine systems of humans and animals

mental hormone disrupters were known mainly for their effects on wildlife, the scientists at the Wingspread meeting concluded that the substances had the potential to cause large-scale dysfunction in humans as well.

In Our Stolen Future, *a new book excerpted here, Theo Colborn and Pete Myers have joined forces with environmental science writer Dianne Dumanoski to survey the problem. They have found that hormone-disrupting chemicals are ubiquitous and that the pathologies they cause may result even from extremely low levels of exposure. Although many synthetic chemicals have been tested for carcinogenic effects, few have been scrutinized for their impact on the human endocrine system. As the authors of* Our Stolen Future *observe, if such substances are causing wide-scale disruption of the hormones that enable us to grow and reproduce, we may be witnessing an evolutionary tragedy in the making.*—B. D. S.

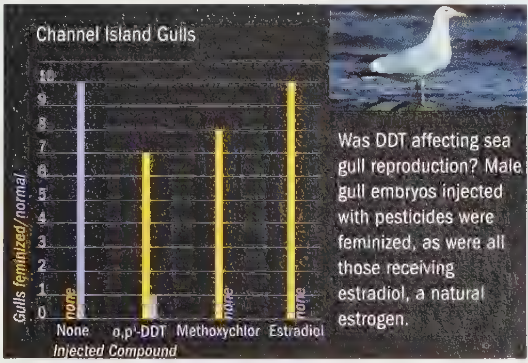


Were mink numbers declining because the animals were fed contaminated fish? Experiments showed that pesticide exposure affected a female mink's fertility.

John Shaw; Bruce Coleman, Inc

The mid-1960s: Lake Michigan

The mink industry that had grown up around the Great Lakes because of the ready supply of cheap fish had begun to falter because of the animals' mystifying reproductive problems. Females weren't producing pups. Michigan State University researchers eventually linked the reproductive failure to PCBs (polychlorinated biphenyls), a family of synthetic chemicals used to insulate electrical equipment. Curiously, a decade earlier, other mink herds in the Midwest had crashed after the animals were fed scraps from chickens that had been given the growth-promoting drug DES. Although the symptoms were strikingly similar to those of the Michigan incident, the second crash of fish-fed mink could not be linked to DES.



Was DDT affecting sea gull reproduction? Male gull embryos injected with pesticides were feminized, as were all those receiving estradiol, a natural estrogen.

John Shaw; Bruce Coleman, Inc

The early 1970s: Channel Islands, Southern California

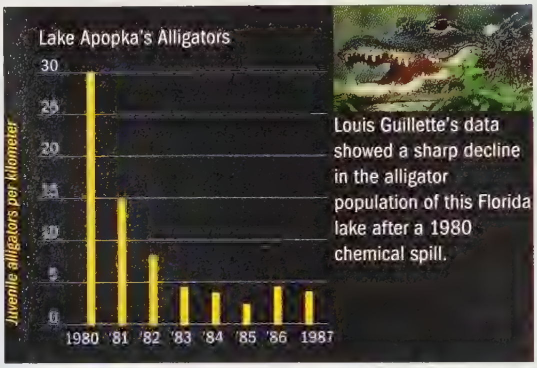
Working on San Nicolas Island in 1968, Ralph Schreiber, of the Los Angeles County Natural History Museum, spotted some gull nests with unusually large numbers of eggs. Since gulls rarely incubate more than three eggs at a time, Schreiber immediately suspected that more than one female was laying in these nests. Four years later, George and Molly Hunt, of the University of California at Irvine, noticed the same phe-

nd John Peterson Myers, 1996 Reprinted by arrangement with Dutton Signet, a division of Penguin Books USA, Inc

nomenon on Santa Barbara Island. They also saw thinning eggshells in the gull colony, leading them to expect the birds were suffering from DDT exposure. Over the next two decades, nesting female pairs would be found among the herring gulls in the Great Lakes, glaucous gulls in Puget Sound, and roseate terns off the coast of Massachusetts. Were the females sharing nests because of a shortage of males?

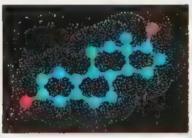
The 1980s: Lake Apopka, Florida

Surveys showed that in some Florida lakes, 90 percent of alligator eggs hatched, but at Lake Apopka the hatching rate barely reached 18 percent. Even worse, half of those that hatched died within ten days. Louis Guillette, a University of Florida reptile biologist, felt there was little question that the problems were linked to a 1980 chemical spill, after which more than 90 percent of the alligators disappeared. But why, after the



Louis Guillette's data showed a sharp decline in the alligator population of this Florida lake after a 1980 chemical spill.

Joe McDonald, Bruce Coleman, Inc

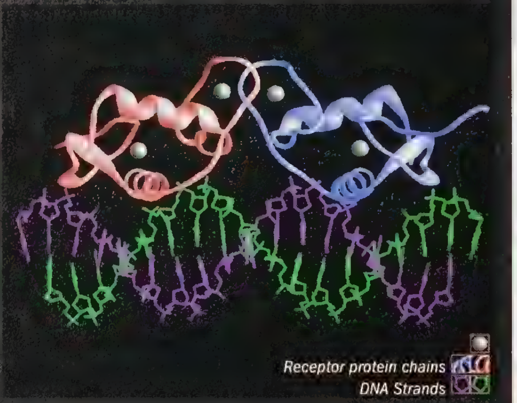


Scientific Computing Group; ACF/NYU· NIEHS

The molecular structure of estradiol, above, is basically the same in all vertebrate animals. Such shared elements of physiology may explain why such a broad range of organisms are similarly vulnerable to environmental hormone disrupters.

The DES Paradigm

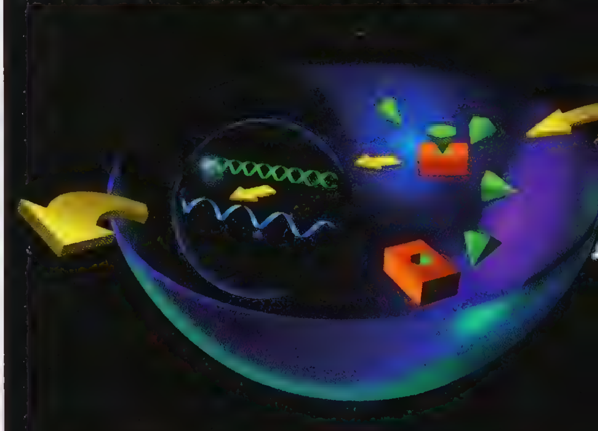
The DNA Bond



John W. R. Schwabe/Protein Data Bank, Brook

Forging the bond Two protein chains from the estrogen receptor bond with a DNA helix. The bonding will trigger replication of proteins that affect reproductive processes.

Receptor Effects of Synthetic Chemicals



Normal response A natural estrogen (green) binds to a receptor within the cell (red rectangle) and activates the DNA in the nucleus to produce the appropriate biological response.

Crossing the tolerance threshold

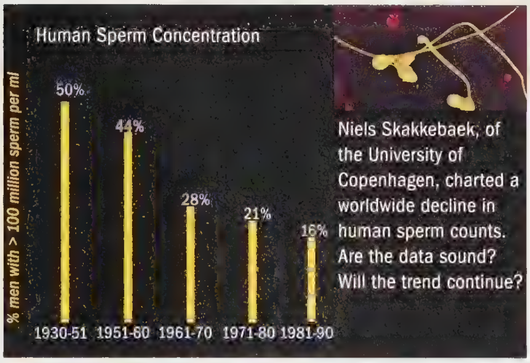
On April 22, 1971, an unusual report appeared in the *New England Journal of Medicine*. A team of doctors from Massachusetts General Hospital had found clear-cell cancer of the vagina—an extremely rare form of cancer that almost never strikes women under fifty—in eight patients, aged fifteen through twenty-two. The doctors also found a common factor. Of the eight patients, seven were daughters of women who had taken the synthetic estrogen diethylstilbestrol (DES) during the first three months of pregnancy.

Developed in 1938, DES was commonly prescribed for women with problem pregnancies in the belief that insufficient estrogen levels caused miscarriages and premature births. In the decades that followed, doctors also began to recommend the drug for untroubled pregnancies, as well as for a number of other conditions ranging from acne to prostate cancer. College clinics also doled out DES as a "morning after" contraceptive, and farmers used tons of the substance in animal feed to fatten livestock.

Regardless of the compelling association between DES and vaginal cancer reported by the Massachusetts General team, some in the medical and scientific communities remained skeptical that a prenatal exposure to DES could cause cancer. The issue was still unsettled when John McLachlan, a young researcher who specialized in the transfer of drugs and other chemicals into the uterus, arrived at the National Institute of Environmental Health Sciences near Raleigh, North Car-waters were again clear, were researchers still finding hatching problems, and why did at least 60 percent of the males have abnormally tiny penises?

1990s: Copenhagen, Denmark

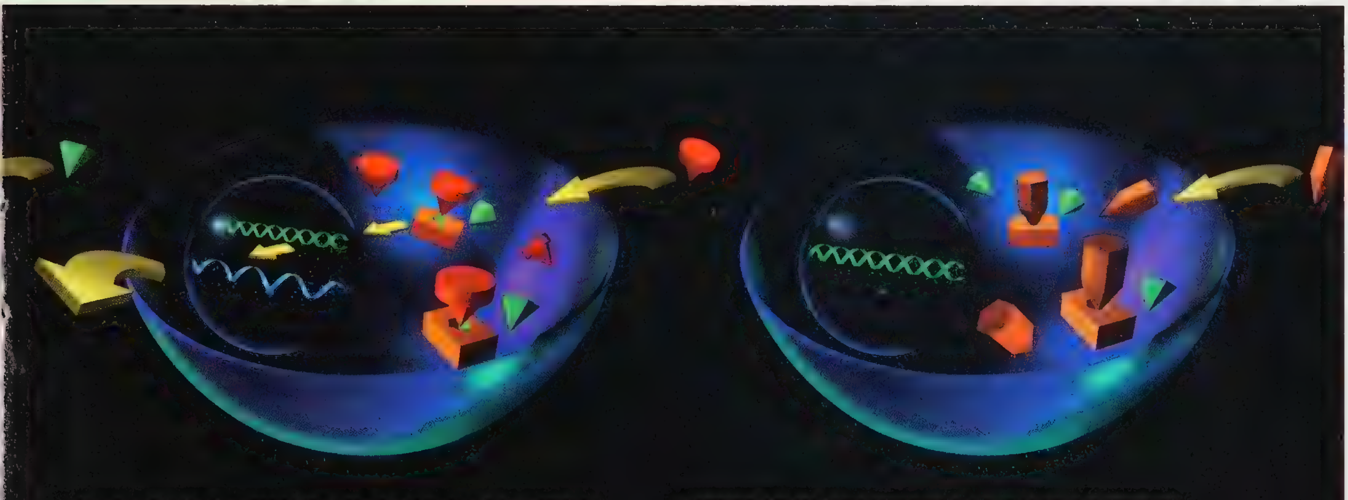
Over the years, Niels Skakkebaek, a reproductive researcher at the University of Copenhagen, had seen more and more human sperm abnormalities, as well as a drop in the typical sperm count. At the same time, Denmark's rate of testicular cancer had tripled. Skakkebaek also noticed low sperm counts and unusual cells in the testes of men who developed this type of cancer. Were the findings connected? He and his colleagues eventually reviewed sixty-one studies, most from the United States and Europe, but also from Asia, South America, and Africa. They were stunned to find that average human male sperm counts had dropped by almost 50 percent between 1938 and 1990. ☐



Niels Skakkebaek, of the University of Copenhagen, charted a worldwide decline in human sperm counts. Are the data sound? Will the trend continue?

Tony Brain, Photo Researchers, Inc

Chart Sources
Eagles. Colborn, *J. Toxicol Environ. H.*, 33 (1991)
Otters: Chanin and Jefferies *Biological Journal of the Linnaean Society* 10 (1978)
Minks: Aulerich et al., *J. Reprod. Fert Suppl.* 19 (1973)
Gulls. Fry and Toone, *Science*, 213 (1981)
Alligators: Louis Guillette, after Woodward et al., 1993
Sperm. Carlsen et al., *BMJ* 305 (1992)



Hormone mimics Organochlorines and other synthetic compounds can also bind to cellular receptors and elicit hormonal responses that may be stronger or weaker than those evoked naturally.

Hormone blocker Some compounds bind with cellular receptors without detectable effects. By outcompeting the natural hormone for receptor sites, however, they suppress natural responses.

Kirk Moldoff, Image Shop/Phototake

olina. In subsequent animal studies, McLachlan and his colleagues demonstrated not only that female mice exposed to DES in the womb eventually developed vaginal adenocarcinoma but also that exposed males turned up with congenital reproductive-system problems, ranging from undescended testicles to abnormal sperm to reduced fertility. DES had somehow interfered with hormonal messages during the rodents' prenatal development.

In the years that followed, ample evidence came to light linking DES not only to human vaginal cancer but also to deformities of the reproductive tract. DES daughters have higher than normal chances of miscarriage, ectopic pregnancy, and premature delivery.

How do hormone mimics such as DES disrupt the endocrine system? To act, a hormone must find—and bind with—the appropriate receptors in and on cells. Once joined to the receptor, hormones move into the cell's nucleus, targeting genes that "turn on" the biological activity associated with the hormone. DES binds to estrogen receptors, which are found inside cells in many parts of the body, including the uterus, breasts, brain, and liver. The synthetic hormone has two troublesome traits. First, it triggers certain parts of the reproductive system more effectively than does estradiol, one of the body's own estrogens. Perhaps even more important, it manages to circumvent a mechanism that protects the fetus from the developmentally disruptive effects of excessive estrogen exposure. Normally, special maternal and fetal blood pro-

John McLachlan's animal studies showed that DES exposure in a pregnant female often resulted in reproductive tract abnormalities in her offspring.

Jerry Ward

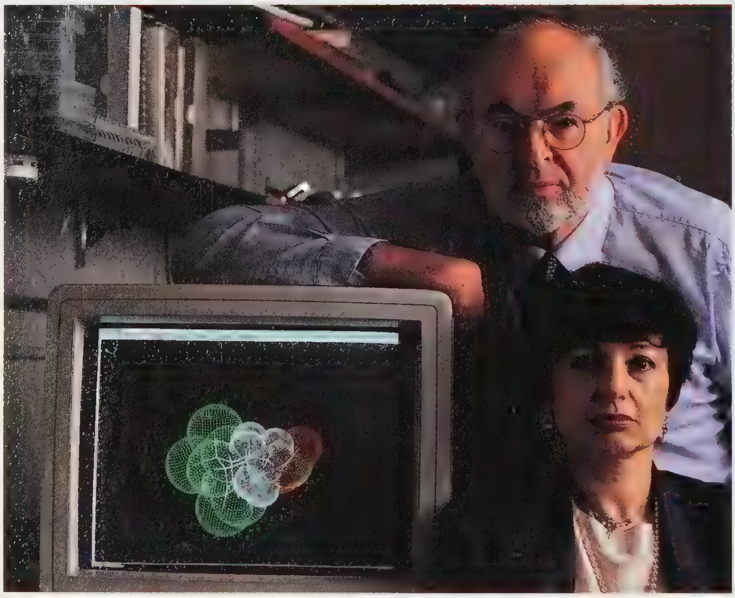
teins soak up almost all excess circulating estrogen. But they do not recognize DES. As a consequence, DES in the fetal blood supply remains biologically active.

How many other human-made chemicals act in this way is a major unanswered question. But evidence suggests that, like DES, other compounds can also make end runs around the body's defense mechanisms. If so, the unborn—whether humans or other animals—are vulnerable to disruption from many quarters.

To date, researchers have identified at least fifty-one chemicals—many of them common—that disrupt hormones in one way or another. Some mimic estrogen as DES does, but others interfere with other parts of the endocrine system, such as thyroid and testosterone metabolism. The tally includes large chemical families—the 209 compounds classified as polychlorinated biphenyls (PCBs), the 75 dioxins, and the 135 furans—that have myriad, documented disruptive effects.

One hundred thousand synthetic chemicals are now on the market around the world. Each year about a thousand new substances are introduced, most of them without adequate testing and review. Some that

Here, There, Everywhere



Bob Sheehan

Their breast-cancer research disrupted by a mysterious contaminant, physicians Ana Soto and Carlos Sonnenschein traced the problem to equipment in their laboratory.

Chasing the plastic imposters

The threat of hormone-disrupting chemicals has come to light largely through a series of accidental discoveries and surprises, but none more bizarre than the incident that took place just after Christmas 1987 at Tufts Medical School in Boston. For more than two decades, physicians Ana Soto and Carlos Sonnenschein had been exploring why cells multiply—a fundamental question in biology, as well as one central to the mystery of cancer, in which cells run amok. Rather than looking for growth factors, however, the two were in hot pursuit of an inhibitor. Assuming that proliferation was the norm, they were trying to find what stops cell growth by experimenting with a strain of human breast cancer cells that multiplies in the presence of estrogen. By 1985, Sonnenschein and Soto had found that if they removed the estrogen from blood serum through a special charcoal-filtering process and then added the serum to estrogen-sensitive breast cancer cells, the cells would stop multiplying. Two years later, they were struggling to isolate and purify the specific substance in the serum that had given the stop signal.

Working with cells in tissue culture can be a tricky business. There is only one way of doing things—impeccably. Any lapse in discipline—the least hint of sloppiness—can ruin weeks, months, even years of work. To eliminate potential problems, Sonnenschein and Soto took elaborate precautions and never had a problem—until that final week of 1987.

Sonnenschein had prepared a series of multiwelled plastic plates, placing breast cancer cells in twelve small cups and then adding varying levels of estrogen or of the estrogen-free serum to the tiny cell colonies. Four days later, the two scientists returned to the lab to see how the cells had fared. According to the routine, they would examine the cells under the microscope before transferring them from the plates to special counting vials for tallying by an electronic particle counter. Over the years, they had done hundreds of variations of this experiment.

Somehow the first plate didn't look right, so Sonnenschein adjusted the microscope and looked again.

have been found harmful have been withdrawn from use in the United States, but according to U. S. customs export records, analyzed by the Foundation for Advancements in Science and Education, in 1991 the United States exported at least 4.1 million pounds of pesticides that have been banned, restricted, or voluntarily withdrawn from use domestically. Overall, exports included 40 million pounds of compounds known to be endocrine disrupters.

Yearly, five billion pounds of pesticides are applied worldwide, not only to agricultural fields but also in parks, schools, restaurants, supermarkets, homes, and gardens. Although synthetic chemicals now seem an inextricable part of the fabric of modern life, they have only come into use fairly recently.

Now scientists are finding evidence that hormone-disrupting chemicals may have combined effects and that seemingly insignificant quantities of individual chemicals can have a major cumulative effect. The magnitude of this problem is still unknown, but those who have watched the list of hormone disrupters grow think the age of discovery is far from over. □

James Joern

The whole plate—every single colony growing in the specially modified blood serum—was as crowded as a subway train at rush hour. The estrogen-sensitive breast cancer cells were not only multiplying, but they were doing so regardless of whether estrogen had been added. In all their years of cell work, Soto and Sonnenschein had never seen anything like it. Something had gone seriously wrong. It had to be some sort of estrogen contamination, because non-estrogen-sensitive cells in other experiments were behaving as expected.

Carefully preparing another batch of plates with breast cancer cells, the two scientists again saw galloping proliferation. It wasn't a fleeting event. The mysterious source of contamination had to be somewhere in the lab. To trace it would mean a tedious process of elimination. It would be four long, frustrating months of checking and rechecking procedures and equipment before the two finally tracked down a source—and two whole years before they were able to put a name to the chemical contaminant that was causing the cells to proliferate. The source was the orange-capped Corning centrifuge tubes that the researchers had always regarded as benign and inert. But something in the tubes appeared to be biologically active.

These findings prompted Sonnenschein and Soto and other Tufts representatives to meet with Corning officials on July 12, 1988. At that meeting, Soto and Sonnenschein learned that Corning had recently modified the composition of the plastic resin in the tubes to make them less brittle. The company had not changed the catalog number on the item, however. When Soto asked about the chemical content of the new resin, Corning declined to disclose the information on the grounds that it was a "trade secret."

Worried about the possible broader implications of their discovery, Sonnenschein and Soto determined to purify the offending compound and to make a preliminary identification using mass spectrometry analysis. Finally, at the end of 1989 they had a definitive answer: the active component in the plastic was p-nonylphenol, part of a family of synthetic chemicals known as alkylphenols and commonly added to polystyrene and polyvinyl chlorides (PVCs) to make them more stable and less breakable. The plastic centrifuge tubes in which Soto and Sonnenschein had stored serum had been of polystyrene—a plastic that, depending on the manufacturer, may or may not contain nonylphenol.

Searching the scientific literature, the investigators found bits and pieces of information that only heightened their concern. One study reported that PVCs containing alkylphenols were used in the food-processing and food-packaging industries. Another investigation found nonylphenol contamination in water that had passed through PVC tubing. Soto and Sonnenschein even discovered that nonylphenol had been used in synthesizing nonoxynyl-9—a compound in contraceptive cream. Yet another experiment demonstrated that nonoxynyl-9 broke down into nonylphenol in laboratory rats.

To ascertain whether p-nonylphenol acted like an estrogen in living animals—not just in a lab dish—Soto and Sonnenschein injected the substance into rats.

They found that in female rats without ovaries, p-nonylphenol caused the lining of the uterus to proliferate (as would have happened had the animals been given natural estrogen).

The researchers also learned that alkylphenol polyethoxylates (chemicals found in many detergents, pesticides, and personal-care products) can break down into nonylphenol and other chemicals that mimic estrogens when they encounter bacteria in animals' bodies, in the environment, or in sewage treatment plants. Although alkylphenol polyethoxylates have been in wide use since the 1940s, they came under scrutiny in the 1980s because of their toxic effect on aquatic life. By the late 1980s, several European countries had already banned their use. In 1990, the United States was still using more than 450 million pounds annually.

When Soto and Sonnenschein published their findings in 1991, even veteran investigators of hormone-disrupting chemicals were shaken. For years, the ongoing discussion about possible human health risks from synthetic chemicals had been based on the assumption that most human exposure comes from chemical residues, primarily pesticides, in food and water. Now Soto and Sonnenschein had discovered hormone disrupters where you would least expect them—in ubiquitous products made from materials considered benign and inert. Here was glaring evidence of our vast ignorance about the dangers in our everyday environment.

While Soto and Sonnenschein were chasing contamination in their lab, a similar drama was unfolding at the opposite end of the country, at Stanford University School of Medicine in Palo Alto, California. In this case, too, an estrogen-mimicking compound was traced to plastic lab equipment—but the culprit substance had not been linked with polystyrene products or nonylphenol. The Stanford team found another estrogen mimic, bisphenol-A, leaching from polycarbonate, an entirely different kind of plastic. Polycarbonate is used in the manufacture of lab flasks, as well as many consumer products, such as the giant jugs used to bottle drinking water.

Here again, the discovery was accidental and occurred only because the scientists were conducting research with estrogen-sensitive cells—in this case, yeast. In the course of their experiments, the Stanford researchers, headed by endocrinologist David Feldman,

Altered Destinies

Up against evolution

Because our knowledge of hormone receptors has grown rapidly since they were first identified in the mid-1960s, we are now beginning to understand why synthetic chemicals have such dramatic effects across an astonishing range of species. Classic accounts of evolution tend to emphasize innovation and change, but there has also been a strong conservative streak in the history of life on Earth.

As scientists have explored hormone chemistry in various animals, they have marveled at the lack of change over millions of years of evolution. Whether in a turtle, a mouse, or a human, the endocrine system produces a chemically identical form of estrogen—estradiol—that binds to an estrogen receptor. The discovery of similar estrogen receptors in animals as different as turtles and humans argues for an endocrine system that arose early in the evolution of vertebrates.

Although research has demonstrated that imposter chemicals bind with the estrogen receptor, it has not yet illuminated why the receptor readily accepts them. The similar effects of DDT and DES led scientists to suspect a common structural feature, but to their bewilderment, they found that the receptor binds to chemicals with strikingly different structures.

The problem is large, and it is by no means restricted to environmental estrogens. Other classes of chemicals affect different parts of the endocrine system, such as thyroid- and testosterone-mediated processes. Still others inhibit the body's ability to produce steroid hormones in the first place.

The pressing question is whether humans are already suffering damage from half a century of exposure to endocrine-system disrupters. Have these chemicals already altered individual destinies by scrambling the chemical messages that guide development? Many of those familiar with the scientific case believe the answer is yes. But whether hormone-disrupting compounds are also having a broad impact across the human population is difficult to assess and even harder to prove. This is so because of the nature of the contamination, the transgenerational effects, and the long lag time before damage becomes evident.

The chemical age has created products, institutions, and cultural attitudes that require synthetic chemicals to sustain them. The task that confronts us over the next half century is one of redesign. We must find safer ways to meet human needs. As we work to create a future where children can be born free of chemical contamination, our scientific knowledge and technological expertise will be crucial. Nothing, however, will be more important to human well-being and survival than the wisdom to appreciate that however great our knowledge, our ignorance is even greater. □

found a contaminant binding to a yeast protein. The estrogen mimic proved to be the bisphenol-A in the lab flasks they used to sterilize water.

In a 1993 paper, the Stanford team reported their discovery and their discussions with the manufacturer of the polycarbonate, GE Plastics Company. Apparently aware that bisphenol-A leaches out, particularly if exposed to high temperatures and caustic cleaners, the company had developed a special washing regimen to eliminate the problem. Stanford began working with GE and soon discovered that the company's chemical assay could not detect bisphenol-A at levels below ten parts per billion. Yet two to five parts per billion of bisphenol-A was enough to prompt an estrogenic response in cells in the laboratory. GE officials contended, however, that polycarbonate containers are unlikely to leach bisphenol-A in normal use because they would not be subject to the high temperatures required for sterilization.

Spurred by the Tufts researchers' report of biologically active plastics, scientists at Spain's University of Granada decided to investigate the plastic coatings that manufacturers use to line metal cans. These often inconspicuous coatings are because of concerns that metals might contaminate the food or impart a metallic taste. Such plastic linings are reportedly found in 85 percent of food cans in the United States and about 40 percent of those sold in Spain. The brother-and-sister team of María-Fátima Olea, a food toxicologist, and Nicolás Olea, a physician specializing in endocrine cancers, analyzed twenty brands of canned foods purchased in the two countries. They discovered bisphenol-A (the same chemical that Stanford researchers had found leaching from polycarbonate lab flasks) in stunningly high concentrations in such canned foods as corn, artichokes, and peas. Bisphenol-A contamination was detected in about half the canned foods they analyzed. In some instances, the cans contained as much as eighty parts per billion—twenty-seven times the amount that the Stanford team reported was enough to make breast cancer cells proliferate. Even though synthetic estrogens are less active than natural hormones, at such levels they may be contributing significantly to human exposures. Biologically active plastics were leaching from "metal" cans, where one would not expect to find plastic at all. □

Carson Redux

Theo Colborn creates her own legacy

When Theo Colborn arrived in the District of Columbia in 1985, a fifty-eight-year-old grandmother with a brand new Ph.D. in zoology, she had no particular interest in biological effects of synthetic chemicals. She had been a pharmacist in New Jersey and a sheep rancher in Colorado before she decided to fulfill a long-held desire—to go to graduate school to study ecology. Through a lifelong passion for watching birds, she had been drawn into the growing environmental movement and had spent years working as a volunteer on western water issues. Although some male advisers had been skeptical about investing energy in a fifty-something graduate student, Colborn persisted and won a slot as a congressional fellow at the Office of Technology Assessment.

Colborn next joined a project at the Conservation Foundation, a nonprofit think tank in the District of Columbia, to assess the health of the Great Lakes. Although the lakes' waters had improved markedly thanks to environmental regulation, Colborn's search through the scientific literature led her to believe that serious problems remained. Blinded like others by a preoccupation with cancer—which in the past three decades has become synonymous with the words "toxic chemicals"—Colborn at first missed important clues.

Gradually, however, she began to see patterns emerging from the studies. The animals with the greatest problems proved to be top predators, such as lake trout, snapping turtles, and bald eagles. And although adult animals often appeared to be doing fine, their offspring had myriad problems—primarily matters of derailed development.

Colborn then began to investigate the human-made contaminants found in the tissues of troubled wildlife. She found evidence in the scientific literature to confirm her hunch that many of these contaminants were disrupting hormones that regulate the body's vital processes and guide development. Seven years later, Colborn is still on the trail of hormonally active chemicals, exploring the implications of such contamination for wildlife and human health.—*Dianne Dumanoski*

DISCOVERY/KAROO

When the Desert Was Green

South Africa's Karoo yields fossils of formidable plant eaters

By Gillian King

A few years ago, paleontologists exploring the desertlike Karoo region of South Africa came upon some curious coiled tubes in the area's 250-million-year-old rocks. Some twenty-four inches in length and six to eight inches in diameter, these fossilized corkscrews led to enlarged chambers within the rocks. The most common fossil animal found in the area's rocks—and the right size to have occupied the corkscrews—was *Diictodon galeops,* a far-distant relative of mammals. Thanks to its abundance in Karoo fossils, this creature is one of the best-known extinct vertebrates. *Diictodon* adults were the size of small dogs and had rather long, slinky bodies. Thousands of specimens of young as well as adults and of rare body skeletons as well as numerous skulls, have been unearthed.

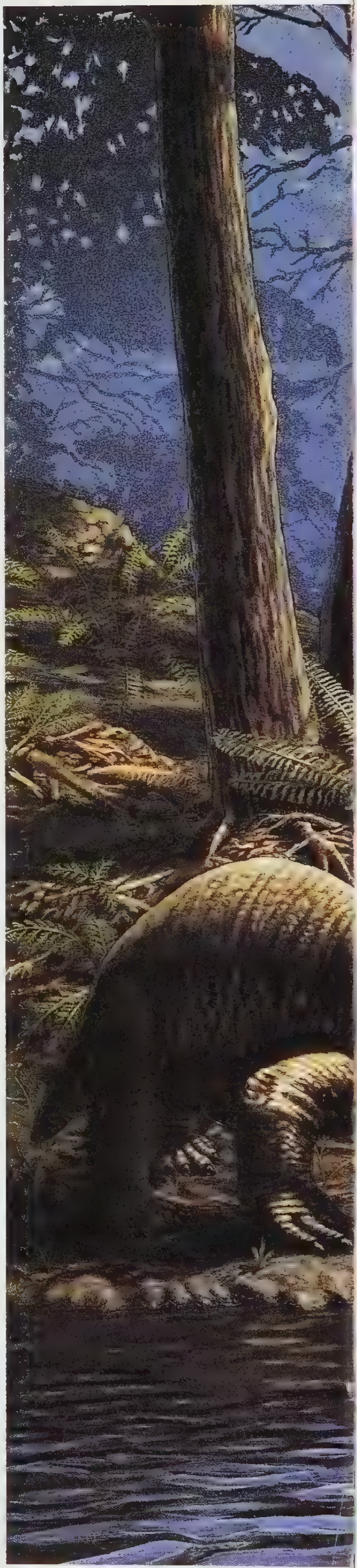
The corkscrews appear to be the spiral entrances of burrows that led to the animals' sleeping or brooding chambers. Although we don't know for certain whether *Diictodon* excavated the burrows or borrowed them from other animals, scratch marks within the burrows are consistent with the animal's using its blunt claws and horny beak to dig the spiral passages.

Diictodon belonged to a group of animals known as dicynodonts. Unlike the polecat-shaped *Diictodon,* most dicynodonts were squat, barrel-bodied, lumbering beasts that ranged from rat size to hippo size. Their front legs sprawled out from the chest, while their back legs were more upright and pulled in partly under the body. Not built for speed or agility, they

Karoo, Cape Province

The stark Karoo landscape is broken only occasionally by the odd bush or sheep or by flat-topped hills, known as kopjes, *where the rocks have weathered to reveal gray, green, and purplish layers.*

Marta Hagglund



The Karoo was once a landscape of fern- and cycad-lined rivers. In a reconstruction of a 245-million-year-old scene, right, one Lystrosaurus *grazes while its companion bathes. The toothy predator* Moschorhinus *lurks in the background.*

THU 15:54 FAX 908 298 3294   SCHERING PLOUGH RESEARCH   ☑001

Schering-Plough
Research Institute

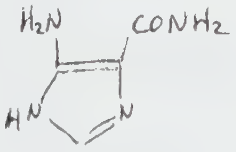
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000

March 28, 1996

Dr. Alfred Bader
Milwaukee, Wisconsin
FAX 414-277-0709

Dear Dr. Bader:

It was so good to talk to you again and to hear about your upcoming trip to Czechoslovakia. As discussed we need to source AIC (below) or the penultimate intermediate to AIC and Lachema in Czechoslovakia is listed as a source. It is so kind of you to offer to carry it here for us but we are in need of ~100kg!



AIC

16496-8

Amino-imidazolecarboxamide

I understand that you may be able to help via your contacts in Czechoslovakia. Thanks for your assistance.

Sincerely,

Martin Stein

Martin Steinman, Ph.D.
Director, Chemical Development

MS/evs

Copy for Prof L. Skursky

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

January 31, 1996

Dr. Edward G. Shaskan
278 Tunxis Road
West Hartford, CT 06107

Dear Dr. Shaskan:

You have a strange telephone line. I tried to phone you several times late in the afternoon as suggested by you, and always just got a recording saying that the number is not operative.

Thank you for your 11-page fax sent to me last week-end, which I have of course studied in detail. The preparation of the racemic nicotinylalanine does not look tremendously difficult, and the most bothersome part is the purification by chromatography involved. Hopefully, that might be avoided on scale up.

I discussed this at length with Hank Koppel, who is unfortunately not at all well, and he is taking early retirement. He pointed out to me that Aldrich quoted to you and wouldn't have done that if the chemists involved had not been confident that Aldrich could indeed make this.

I then discussed this with Dr. Clinton Lane, the executive vice president at Aldrich and shared with him your letter describing this very interesting product.

May I suggest that you telephone Dr. Lane and determine whether Aldrich might not revise its quotation and then accept your order?

One problem that you do of course have is that you operate alone and not in a company whose credit rating is well-established.

If Dr. Lane sounds helpful, then I would advise you to come to Milwaukee and discuss the practical details, such as your credit, with Aldrich personally.

With all good wishes, I remain,

Yours sincerely,

AB/cw

c: Clint Lane

Edward G. Shaskan, Ph.D.
278 Tunxis Road
West Hartford, Connecticut 06107
(860) 561-0040 Telephone or FAX

FAX Total Pages = 11

To DR. CLINTON LANE 1-414-459 498

To: **Dr. Alfred R. ~~Bader~~**
Milwaukee, Wisconsin

DR. CLINTON LANE

Date: **January 26, 1996**

Re: **GMP Synthesis of 2S-Nicotinylalanine**

Nicotinylalanine (also referred to as γ-(3-pyridyl)-γ-oxo-α-aminobutyrate) has the empiric formula $C_6H_{10}N_2O_3$ with MW = 194.1 Daltons. The compound has an asymmetric carbon atom and accordingly exists in enantiomeric (2R and 2S) or racemic forms. Although the racemic mixture has activity as a competitive inhibitor of the enzyme kynureninase (see Decker et al., 1963; appended), the 2S conformation is the preferred stereoisomer. However, presently there seems to exist no efficient direct method for obtaining production levels of the isomer and, therefore, all of our pharmacological experiments have been with the racemer. For the purpose of commercial production, however, the racemer should be resolvable into its isomers by conventional means followed by fractional crystallization of the active 2S-nicotinylalanine.

We have reached the stage in preclinical testing such that communications have begun with the FDA in order to facilitate further development leading to toxicity testing in humans (Phase I, IND). Expected additional toxicity testing in mice will pose no constraints on quantity of drug but 90-day testing in dogs will consume a minimum of 10 Kilograms of drug (20 Kg. to be on the safe-side). Optimistic that the drug will have few signs of toxicity (we have seen none in i.v. pharmacokinetic studies in mice at doses up to 400 mg/kg) and encouraged by results from our preclinical efficacy studies, we are hopeful that the FDA will approve a Phase I Study (toxicity) in patients within this year. Therefore, we are seeking a reputable source for GMP-Production of 2S-Nicotinylalanine. The current method(s) yield 2RS-Nicotinylalanine-dihydrochloride, as provided for us by Pharm-Eco Laboratories, Inc. (Lexington, Mass.).

Given this background, perhaps we could talk over the telephone again before coming to terms. My home phone answering device is attached to a FAX machine and I am mostly available at my home office between 3 to 6 PM EST.

Thank you for your consideration in this matter.

Sincerely,
Ed

LIT. JOC, 28, 383 (1963)
J. BIOL CHEM., 238, 1049 (1963)

Edward G. Shaskan, Ph.D.
[illegible]
West Hartford, Connecticut 06[illegible]
(860) 561-0040 Telephone or FAX

FAX Total Pages = 11

To: **Dr. Alfred R. Bader**
Milwaukee, Wisconsin

Date: **January 26, 1996**

Re: **GMP Synthesis of 2S-Nicotinylalanine**

Nicotinylalanine (also referred to as γ-(3-pyridyl)-γ-oxo-α-aminobutyrate) has the empiric formula $C_6H_{10}N_2O_3$ with MW = 194.1 Daltons. The compound has an asymmetric carbon atom and accordingly exists in enantiomeric (2R and 2S) or racemic forms. Although the racemic mixture has activity as a competitive inhibitor of the enzyme kynureninase (see Decker et al., 1963; appended), the 2S conformation is the preferred stereoisomer. However, presently there seems to exist no efficient direct method for obtaining production levels of the isomer and, therefore, all of our pharmacological experiments have been with the racemer. For the purpose of commercial production, however, the racemer should be resolvable into its isomers by conventional means followed by fractional crystallization of the active 2S-[illegible]

We have reached the stage in preclinical testing such that communications have begun with the FDA in order to facilitate further development leading to toxicity testing in humans (Phase I, IND). Expected additional toxicity testing in mice will pose no constraints on quantity of drug but 90-day testing in dogs will consume a minimum of 10 Kilograms of drug (20 Kg. to be on the safe-side). Optimistic that the drug will have few signs of toxicity (we have seen none in i.v. pharmacokinetic studies in mice at doses up to 400 mg/kg) and encouraged by results from our preclinical efficacy studies, we are hopeful that the FDA will approve a Phase I Study (toxicity) in patients within this year. Therefore, we are seeking a reputable source for GMP-Production of 2S-Nicotinylalanine. The current method(s) yield 2RS-Nicotinylalanine-dihydrochloride, as provided for us by Pharm-Eco Laboratories, Inc. (Lexington, Mass.).

Given this background, perhaps we could talk over the telephone again before coming to terms. My home phone answering device is attached to a FAX machine and I am mostly available at my home office between 3 to 6 PM EST.

Thank you for your consideration in this matter.

To DR CLINTON LANE 1-414-459 4909

LIT JOC, 28, 387 (1963)
J. BIOL. CHEM., 238, 1049 (1963)

log K_1
-1.460
-1.359
-1.369
-1.510
-1.574
-1.130
-0.023
.800
1.117
0.00

l angles of
The result
aching th
m.[17] High
1550–1700
ported in a

tanones.—N
eld by dir
in refluxing
mole) of
dioxane solu
1 mole) w
wed to stan
mixture wa
oric acid was
The mixtur
lium chlori
phases. Th
n bicarbonat
drous sodiu
the followin
are listed in
istilled. The
e (1 mm) t
y fractiona
The oil was
aqueous co
night. Th
r, and dried
hydrochloric
er layer was
e residue was
ve crystalline
lid not occur
easure to ob
with exces
night. The
h ether, and
isolated fro
ladsi in "Sym-
Press London
es were deter-
1482 (1956).

INFRARED SPECTRA OF SOME BENZOYLCYCLOPENTANONES

Compound	X	Tautomer[a]	°C.	unconj.	conj.	C=C region
I	H	Keto[b]	Liq.	1742 s	1688 s	1640-1510[d]
VII	p-OCH_3	Enol[c]	70–72	1738 vw		1640 m, 1605 s, 1600 m
VII	p-OCH_3	Keto[b]	63–64	1740 s	1682 s	1605 s
VIII	p-NO_2	Enol[c]	79–80			1640 s, 1605 m
VIII	p-NO_2	Keto[b]	88–89		1685	1650, 1615

[a] No OH band in the 3000–4000-cm.$^{-1}$ region for either tautomer. [b] Colorless. [c] Yellow. [d] Hyphen indicates overlapping bands.

the resulting ether extract. Compounds II and XV were distilled; in all other cases employing this procedure the product crystallized directly from hexane, pentane, or ligroin.

Isolation of 2,5-Dibenzoylcyclopentanone (XX).—When the preparation of I was carried out as above, the ether extract from the decomposed reaction mixture was flash distilled and the residue taken up in hot methanol. Cooling of the methanol yielded a trace of yellow crystals of XX,[3] m.p. 121–122°.

Alternative Benzoylation Methods. Acid Chloride.—A solution of 13.9 g. (0.165 mole) of cyclopentanone and 23.0 g. (0.165 mole) of benzoyl chloride in 200 ml. of dry benzene was stirred at 0° under dry nitrogen. Sodium hydride[20] (15 g., 0.33 mole) was added in ten portions with cooling and stirring. The mixture was refluxed for 3 hr. Decomposition and isolation in the usual manner yielded 4 g. of cyclopentanone (2,4-DNP, m.p. 143°), 6 g. of benzoyl chloride, and a few drops of I (b.p. 150–155°/7 mm.).

Methyl Ester Method.—A dispersion of 17.8 g. (0.33 mole) of sodium methoxide in 300 ml. of benzene was stirred as 13.9 g. (0.165 mole) of cyclopentanone was added over a 10-min. period. After 5 min. more, 22.5 g. (0.165 mole) of methyl benzoate was added over a 10-min. period. The mixture was allowed to stand for 0.5 hr. and heated on a steam bath overnight. The mixture was decomposed and the product isolated by procedure C above. Yellow crystals from n-hexane were identified as 2-benzoyl-5-cyclopentylidenecyclopentanone (XXI), 2 g., m.p. 99–100°.[19] No other product was isolated.

Phenyl Ester Method.—The procedure for preparation of aroylcyclohexanones[3] was applied to phenyl anisoate and cyclopentanone. Isolation procedure C above yielded 7 g. of copper chelate, from which 4 g. of 2-(p-anisoyl)-5-cyclopentylidenecyclopentanone (XXII) was isolated, m.p. 104–106°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.90; H, 7.52.

Determination of Percentage Enol.—The enol content was determined at equilibrium. A weighed sample of diketone (approximately 0.2 g.) was dissolved in 50 ml. of anhydrous absolute methanol. The solution was allowed to stand for 48 hr. at room temperature in the dark. The modified bromine titration[3,21] procedure was used to determine percentage enol. Due to a shifting end point, the titration was carried out rapidly arriving at the end point within 2 min. for consistent results. The results of the determinations are listed in Table II.

Measurement of Spectra.—The infrared spectra were measured using a Perkin–Elmer Model 21 double-beam recording spectrophotometer with a sodium chloride prism. The control settings were maintained constant at: resolution, 926; response 1; gain 5; speed, 4; suppression, 4. The concentration used was 40 mg./ml. Matched 0.1-mm. cells were used in standard double-beam operation. Data obtained are listed in Table IV.

---

(20) A [illegible]2% mineral oil dispersion was first washed with benzene in a dry nitrogen atmosphere to give oil-free sodium hydride, which was used immediately.

(21) W. T. Smith, Jr., and R. L. Shriner, "The Examination of New Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p

JOC 28, 383 (1963)

The Synthesis of Hydroxycotinine and Studies on Its Structure[1]

HERBERT MCKENNIS, JR., LENNOX B. TURNBULL, EDWARD R. BOWMAN,[2] AND EINOSUKE TAMAKI[3]

Department of Pharmacology, Medical College of Virginia, Richmond, Virginia

[illegible]

Hydroxycotinine, an optically active metabolite which arises *in vivo* from (−)-nicotine by way of the intermediate (−)-cotinine, was converted to chlorocotinine by reaction with thionyl chloride. The resultant chlorocotinine yielded (−)-cotinine upon hydrogenolysis. (3-Pyridyl)-γ-oxo-α-acetamidobutyric acid, prepared from acetamidomalonic ester and bromomethyl 3-pyridyl ketone, was converted with methylamine and hydrogen in the presence of Raney nickel to acetamidocotinine. Aminocotinine from hydrolysis of the latter afforded two isomeric pairs of hydroxycotinine. The dextrorotatory form obtained by resolution of one of these pairs corresponded in melting point, mixed melting point, and infrared absorption spectra to metabolic hydroxycotinine.

In the metabolism of (−)-nicotine in the dog, oxidation of the pyrrolidine ring leads to the formation of)-cotinine, 5-(3′-pyridyl)-1-methylpyrrolidone-2.[4] Metabolism of (−)-cotinine gives rise[5-7] in turn to a number of additional pyridino compounds which through the ubiquitousness[8] of cotinine, may be common to a number of species.

During early studies[6] on the metabolism of (−)-cotinine in the dog a fraction giving a strong Koenig reaction and containing two components was obtained. One component was identified in crystalline form as (−)-demethylcotinine. The other metabolic component was acetylated with acetic anhydride in pyridine and then yielded a crystalline picrate, $C_{18}H_{17}N_5O_{10}$. The acetylated metabolite, acetoxycotinine, gave[7] upon acidic hydrolysis a colorless alcohol, hydroxy-

---

(1) Aided by grants from the Tobacco Industry Research Committee and the American Tobacco Co. Presented in part at the Division of Biological Chemistry, 135th National Meeting of the American Chemical Society, Boston, Mass., April 6, 1959.

(2) Public Health Research Fellow of the National Heart Institute, National Institutes of Health.

(3) American Tobacco Research Fellow. Present address: Japan Monopoly Corp., Tokyo, Japan.

(4) H. McKennis, Jr., L. B. Turnbull, and E. R. Bowman, *J. Am. Chem. Soc.*, **80**, 6597 (1958).

(5) H. McKennis, Jr., L. B. Turnbull, E. R. Bowman, and E. Wada, *ibid.*, **81**, 3951 (1959).

(6) H. McKennis, Jr., E. R. Bowman, and L. B. Turnbull, *Proc. Soc. Exptl. Biol. Med.*, **107**, 145 (1961).

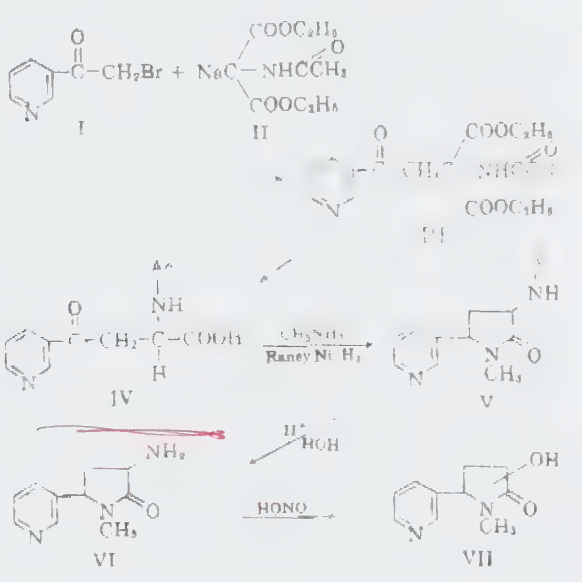
(7) E. R. Bowman and H. McKennis, Jr., *J. Pharmacol. Exptl. Therap.*, **135**, 306 (1962).

(8) (a) F. E. Guthrie, R. L. Ringer, and T. G. Bowery, *J. Econ. Entomol.*, **50**, 822 (1957); (b) H. B. Hucker, J. R. Gillette, and B. B. Brodie, *Nature*, **183**, 47 (1959); (c) R. Truhaut and M. de Clercq, *Bull. soc. chim. biol.*, **41**, 1693 (1959).

cotinine, $C_{10}H_{12}N_2O_2$, $[\alpha]_D$ +42.5° (methanol). The alcohol in turn formed[7] a crystalline picrate, $C_{16}H_{15}N_5O_9$. Hydroxycotinine has also been obtained[9] from the urine of rats following administration of (−)-cotinine and has now been isolated as the derivative acetoxycotinine picrate, from the urine of smokers. The strong Koenig reaction of hydroxycotinine and the failure of the compound to be retained on Dowex 21K (OH⁻) led[5] to the provisional structure in which the metabolite bears an hydroxyl group on the pyrrolidone ring of the parent compound, cotinine. The present report, in which the total synthesis of hydroxycotinine is described, serves to bear out the correctness of this assignment.

Both 3- and 4-hydroxycotinine, 5-(3′-pyridyl)-3-hydroxy-1-methylpyrrolidone-2 and 5-(3′-pyridyl)-4-hydroxy-1-methylpyrrolidone-2 are attractive to consider as possible metabolites and possible inhibitors of the metabolism of nicotine and related substances. The apparent reversibility of the reaction cotinine → γ-(3-pyridyl)-γ-methylaminobutyric acid *in vivo*[4,10,11] can, furthermore, be hypothetically extended[12] to the hydroxy acids corresponding to 3- and 4-hydroxycotinine.

The synthesis of 3(?)-hydroxycotinine has now been completed by the following series of reactions



Among several possible syntheses the foregoing was attractive since two of the important intermediates, 3-acetylpyridine, the intermediate for preparation of the bromomethyl pyridyl ketone, and acetamidomalonic ester are commercially available.

Bromomethyl 3-pyridyl ketone (I) as the hydrobromide or hydrochloride was condensed with sodioacetamidomalonic ester (II) to yield the desired 2-nicotinylmethyl 2-acetamidomalonic ester (III). The latter upon basic hydrolysis yielded γ-(3-pyridyl)-γ-oxo-α-acetamidobutyric acid (IV). The ammonium salt of this acid in the presence of methylamine, hydrogen, and Raney nickel afforded 3-acetamidocotinine (V). This acetamido compound was readily hydrolyzed to 3-aminocotinine (VI). The latter was diazotized in sulfuric acid to obtain hydroxycotinine (VII).

In the foregoing synthesis the steps leading from bromomethyl 3-pyridyl ketone through 3-aminocotinine are regarded as unequivocal although degradations were not effected. In the diazotization of 3-aminocotinine to hydroxycotinine, 3-hydroxycotinine is considered the most likely product, although intramolecular rearrangements do accompany diazotization reactions. The assignment of the hydroxyl group to the 3-position of the pyrrolidone ring indicates, therefore, a probability and is not decisive in the absence of degradations and other corroborating investigations.

Aminocotinine (VI), which was not examined for possible diastereoisomeric forms, yielded upon diazotization hydroxycotinine which contained two isomeric pairs. These were separated by fractional crystallization. The high-melting form was converted to a chlorocotinine by reaction with thionyl chloride. Upon hydrogenolysis this chlorocotinine yielded (+, −)-cotinine, identified as the monopicrate in comparison with an authentic synthetic sample.

Resolution of the high-melting form of hydroxycotinine with tartaric acid led to the isolation of a dextrorotatory enantiomorph, m.p. 135–137°. The compound, which differed from metabolic (+)-hydroxycotinine in melting point, was cochromatographed on paper with the metabolic product in two solvent systems.[13]

The low-melting form of synthetic hydroxycotinine upon resolution with tartaric acid, yielded a dextrorotatory product, m.p. 110–111°, $[\alpha]$ +47.30°. The melting point and R_f value agreed with that of the metabolic product. Upon admixture of the synthetic and natural product there was no melting-point depression. The close correspondence of the infrared absorption spectra[14] of the metabolic and effectively totally synthetic compounds provided further evidence for the identity of the natural and synthetic compounds.

Metabolic hydroxycotinine was converted to chlorocotinine by treatment with thionyl chloride. The chlorocotinine, upon hydrogenolysis, yielded (−)-cotinine which was characterized as the hydrobromide and compared with an authentic sample.

If it is considered that the hydroxyl group of metabolic hydroxycotinine is in position 3 (or 4) on the pyrrolidone ring—and position 3 appears likely on the basis of the synthetic method—the compound contains two asymmetric centers. The reduction of the chlorocotinine which was obtained from metabolic hydroxycotinine to (−)-cotinine would then indicate that in the metabolism of (−)-cotinine to hydroxycotinine the absolute configuration of the 5-carbon of the pyrrolidone ring of (−)-cotinine has been retained. Previous studies have shown[4] that this carbon atom of (−

---

[9] H. McKennis, Jr., L. B. Turnbull, S. L. Schwartz, E. Tamaki, and F. R. Bowman, *J. Biol. Chem.*, **237**, 541 (1962).

[10] H. B. Hucker and J. R. Gillette, *Federation Proc.*, **19**, 30 (1960).

[11] H. McKennis, Jr., L. B. Turnbull, H. N. Wingfield, Jr., and Dewey, *J. Am. Chem. Soc.*, **80**, 1634 (1958).

[12] In this connection it is interesting to note that R. H. Decker and R. R. Brown [*Federation Proc.*, **21**, 3 (1962)] have found that γ-(3-pyridyl)-γ-oxo-α-aminobutyric acid, derivable from one of the intermediates in our synthesis of hydroxycotinine, is an inhibitor of kynureninase and kynurenine hydroxylase.

[13] The compositions of the solvent systems which are designated "acid" and "base" in this paper have been previously described (ref. 5).

[14] The authors are grateful to Mr. J. Scott Osborne of the Department of Research and Development, The American Tobacco Co., for the determinations.

cotinine has the same absolute configuration as that of the parent compound L-(−)-nicotine.

Experimental

Bromomethyl 3-Pyridyl Ketone Hydrobromide.—To a solution of 3-acetylpyridine (2.5 g.) in 25 ml. of 48% hydrogen bromide in glacial acetic acid was added 7.2 g. of pyridine hydrobromide perbromide with stirring. The white crystalline product separated. Precipitation was completed by addition of ether. The salt was collected, washed with ether and was air-dried (5.5 g., 92%). The product, which was sufficiently pure for condensation, was further purified by several recrystallizations from methanol–ether, m.p. 185–188° dec.

Anal. Calcd. for $C_7H_7NOBr_2$: C, 29.72; H, 2.51. Found: C, 29.79; H, 2.81.

The foregoing procedure appears to be more convenient than that employed by Wingfield,[16] who prepared the hydrobromide of bromomethyl 3-pyridyl ketone and presented analytical data, but no melting point.

A product, apparently a mixture of the hydrobromide and hydrochloride salts, which is also satisfactory for condensation reactions, was prepared from a solution of 3-acetylpyridine (45.6 g.) in 445 ml. of glacial acetic acid saturated with hydrochloric acid. Pyridine hydrobromide perbromide (130.5 g.) was added in one portion, and the mixture was mechanically stirred until precipitation of the colorless crystalline product was complete. The crystals were collected, washed once with methanol–ether (1–1 by vol.) and finally with ether. The air-dried product (87 g.), which was used directly or stored in diffuse light, was used interchangeably (on a weight basis) with the hydrobromide (above).

Ethyl γ-(3-Pyridyl)-γ-oxo-α-acetamido-α-carbethoxybutyrate.—To a solution of 233 g. of diethyl acetamidomalonate in 1 l. of absolute ethanol was added 27.7 g. of sodium chips in an atmosphere of nitrogen. After completion of the reaction under reflux, the solvent was removed under diminished pressure. The glassy residue, obtained by drying overnight at 1 mm., was pulverized and then added to a mixture of 1.5 l. of benzene and 145 g. of bromomethyl 3-pyridyl ketone hydrobromide. The mixture was refluxed with stirring for 48 hr. and then filtered. The benzene solution was extracted with 600 ml. of 0.1 *N* hydrochloric acid and then with 200 ml. of 0.1 *N* hydrochloric acid. Acetamidomalonic ester (92 g.) was recovered from the benzene layer. The combined aqueous layers were made alkaline with concentrated ammonia water (60 ml.) and then extracted with two portions of chloroform (500 ml. and 800 ml. each). The deeply colored chloroform layer was concentrated to 200 ml. and then placed on a column of acid-washed alumina (1 kg., Merck & Co., Rahway, N. J.). The column was eluted with 2 l. of methanol–ether (1–20 by vol.) and finally with 2 l. of methanol–ether (1–10 by vol.). The residue from evaporation of the combined eluates yielded, upon recrystallization from benzene–hexane, 105 g. of virtually colorless crystalline ethyl γ-(3-pyridyl)-γ-oxo-α-acetamido-α-carbethoxybutyrate, m.p. 126–128°. The product at this stage was sufficiently pure for hydrolysis and decarboxylation. For analysis a sample was recrystallized several times from benzene–hexane, m.p. 139.5–141.5°.

Anal. Calcd. for $C_{10}H_{20}N_2O_6$: C, 57.13; H, 5.99; N, 8.[illegible] Found: C, 57.07; H, 5.78; N, 8.27.

Ammonium γ-(3-Pyridyl)-γ-oxo-α-acetoamidobutyrate.—Ethyl γ-(3-pyridyl)-γ-oxo-α-acetamido-α-carbethoxybutyrate (m.p. 126–128°, above, 210 g.) was stirred with 1272 ml. of 1.00 *N* sodium hydroxide at room temperature until solution was complete (approx. 2 hr.). Glacial acetic acid (110 ml.) was then added, and the solution was heated to boiling for 20 min. (evolution of carbon dioxide). The cooled solution was then placed upon a column of Dowex 50 (H^+), 2 l. The column was eluted with 2 *N* ammonia water until the eluate gave a negative Koenig reaction. The residue from evaporation of the ammoniacal solution was recrystallized from methanol to give 110 g. of colorless crystals, m.p. 181–182°. For analysis a sample was recrystallized from ethanol–acetone and air-dried, m.p. 181–183°.

Anal. Calcd. for $C_{11}H_{15}N_3O_4$: C, 52.16; H, 5.97; N, 16.59. Found: C, 52.18; H, 6.12; N, 16.7.

3-Acetamido-3-methylcarbamyl-1-methyl-5-(3′-pyridyl)pyrrolidone-2.—A solution of 3.0 g. of ethyl γ-(3-pyridyl)-γ-oxo-α-acetamido-α-carbethoxybutyrate in 40 ml. of methanol was hydrogenated at 32 atm. in the presence of 7.3 g. of methylamine and 1 g. of Raney nickel for 4 hr. at 55°. After removal of the catalyst and the solvent, the residue was recrystallized from methanol to obtain 2.3 g. of colorless crystals, which sintered at 137° and melted at 195.5°, λ_{max} 262 mμ, *k* 9.18 in methanol. The air-dried sample gave the correct analysis for a monohydrate, R_f 0.76 (base) and R_f 0.46 (acid).

Anal. Calcd. for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.53; N, 18.17. Found: C, 54.60, H, 6.87; N, 18.1.

3-Acetamidocotinine.—A solution of 80 g. of ammonium γ-(3-pyridyl)-γ-oxo-α-acetamidobutyric acid (m.p. 181–182°) in 1200 ml. of absolute ethanol was hydrogenated at 80 atm. and 95° in the presence of 8 g. of Raney nickel and 260 g. of methylamine during 8 hr. After removal of the catalyst, the ethanolic solution was evaporated to dryness. The residue was dissolved in chloroform and placed upon a column of acid-washed alumina (1200 g.). Elution with methanol–chloroform (1–20 and 1–10 by vol.) served to remove material showing a single Koenig positive zone (R_f 0.62, base, and R_f 0.32, acid) upon paper chromatography. The residue from evaporation of the combined eluates, a straw-colored gum (48 g.), yielded a crystalline picrate upon treated with a saturated solution of picric acid (15% H_2O) in methanol. For analysis the yellow salt, 5-(3′-pyridyl)-3-acetamido-1-methylpyrrolidone-2 monopicrate, was recrystallized from aqueous methanol (m.p. 247–249°, dec.) and dried at 1 mm. and 50° for 2 hr.

Anal. Calcd. for $C_{18}H_{18}N_6O_9$: C, 46.76; H, 3.92. Found: C, 46.66; H, 3.70.

Hydroxycotinine (Mixed Isomers).—A solution of 144 g. of 3-acetamidocotinine (as the straw-colored gum obtained above) in 1085 ml. of 5 *N* hydrochloric acid was heated under reflux for 5 hr. During the period 3-acetamidocotinine (R_f 0.62, base) was hydrolyzed to aminocotinine (R_f 0.53, base, and R_f 0.17, acid). After cooling, the mixture was made alkaline with sodium hydroxide (216 g.) and then extracted with eight portions of chloroform (950 ml. each). Crude aminocotinine (86 g.) was obtained as a dark gum upon evaporation of the chloroform. Without further purification the aminocotinine was dissolved in 1 l. of 2 *N* sulfuric acid. Sodium nitrite (100 g.) was added slowly with stirring to the solution which was cooled in an ice-salt bath. When the addition was complete the solution was allowed to warm to room temperature and then made faintly alkaline to litmus by addition of sodium hydroxide pellets (approx. 80 g.). The solution was concentrated to 500 ml. under diminished pressure and then extracted with seven portions of chloroform (950 ml. each). The combined chloroform solutions upon evaporation yielded 53 g. of crude hydroxycotinine (A) as a dark viscous gum. The mixture showed upon paper chromatography Koenig positive zones at R_f 0.61 (base) and R_f 0.30 (acid), indicating completeness of diazotization. A minor spot was occasionally observed at R_f 0.70, base.

When the diazotization of 3-aminocotinine was conducted in hydrochloric acid rather than sulfuric acid it was possible to isolate a Koenig positive compound (R_f 0.76, base, and R_f 0.52, acid) which gave the correct analysis for 3-chlorocotinine. The chloroform solution obtained by extraction of the alkalinized diazotization mixture was dried over sodium sulfate and placed on a column of alumina. Elution with chloroform removed a halogen-containing component while hydroxycotinine remained on the column. The crystalline residue from evaporation of the chloroform was rechromatographed on alumina and eluted with methanol–ether to obtain a sample, m.p. 125–126°, which was recrystallized from acetone–hexane, m.p. 135–137°.

Anal. Calcd. for $C_{10}H_{11}N_2OCl$: C, 57.01; H, 5.26; N, 13.30. Found: C, 56.76; H, 5.43; N, 13.22.

Acetoxycotinine.—Crude hydroxycotinine (A) from the diazotization (8.3 g.) was treated with an excess of acetic anhydride in pyridine. After standing overnight the mixture was concentrated at the oil pump. The residue was dissolved in chloroform and placed on a column of acid-washed alumina. The column was eluted with ethanol–chloroform. The first fractions (from 2.5 to 5% methanol) upon evaporation yielded acetoxycotinine as a colorless oil, R_f 0.75 (base). The latter fractions (10% methanol) yielded a small amount of unesterified hydroxycotinine. The acetoxycotinine fraction was converted to a picrate with methanolic picric acid. The yellow salt was recrystallized several times from methanol, m.p. 167–169°, and then dried for 1 hr. at 50° and 1 mm.

---

[15] P. Karrer and R. Widmer, *Helv. Chim. Acta*, **8**, 364 (1925).

[16] Appreciation is expressed to Mr. H. N. Wingfield, Jr., for discussing this work with us prior to publication [*J. Org. Chem.*, **24**, 872 (1959)].

Anal. Calcd. for $C_{18}H_{17}N_5O_{10}$: C, 46.66; H, 3.70; N, 15.12. Found: C, 46.66; H, 3.35; N, 15.15, 15.3.

(+, −)-**Hydroxycotinine Isomer I.**—A sample of the foregoing acetoxycotinine picrate was dissolved in water and placed upon a column of Dowex 50 (H^+). After a water wash to remove picric acid the column was eluted with 0.1 *N* ammonia water until no more Koenig positive material could be obtained. The solution showed upon paper chromatography a single Koenig positive zone (R_f 0.61, base; R_f 0.30, acid). The solution was extracted with chloroform to give a light tan oil which solidified after standing approximately 1 week. The resultant hydroxycotinine was recrystallized from acetone, m.p. 149.5–151°, and dried at 1 mm. and 50°. The same product was also obtained directly from the crude hydroxycotinine (A from the diazotization above). A solution of 31 g. of A in 60 ml. of acetone upon cooling deposited 21 g. of almost colorless crystals, m.p. 127–139°. The solution, after concentration to 30 ml. and upon cooling, deposited an additional crop, 2.2 g., m.p. 99–113°. The mother liquor (B) yielded another isomeric pair as described below. The combined crops were recrystallized five times from methyl ethyl ketone to give 9.0 g., m.p. 146–148°. After several recrystallizations from acetone the product, which was dried at 50° and 1 mm., melted at 149–151°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.57. Found: C, 62.2; H, 6.48; N, 14.25.

(+)-**Hydroxycotinine, High-melting Isomer.**—(+, −)-Hydroxycotinine, m.p. 149.5–151°, (5 g.) and 5 g. of (+)-tartaric acid were dissolved in 28 ml. of methanol. Upon cooling and scratching, a precipitate formed. Two recrystallizations from methanol afforded 3 g. of a tartrate, m.p. 159–161°. The salt was dissolved in 20 ml. of 5 *N* ammonia water, and the solution was extracted with five portions of chloroform (25 ml. each). The oily residue from evaporation of the chloroform crystallized on standing and weighed 890 mg. after two recrystallizations from acetone. The air-dried material melted at 86–128° and formed crystals, m.p. 135–137°, upon drying overnight at 50° and 1 mm.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.57. Found: C, 62.25; H, 6.39; N, 14.40. $[\alpha]^{26}_{546}$ +46.2° (*c*, 10 in methanol).

(+, −)-**Hydroxycotinine, Isomer II.**—The mother liquor (B) from the high-melting isomer (above) was cooled in the refrigerator to give three crops (3.0 g., m.p. 71–72°; 1.1 g., m.p. 70–71.5°; 0.7 g., m.p. 70–71°) and finally 3.0 g. of gum. The combined crystalline crops were recrystallized four times from benzene to give an analytical sample melting at 70.5–72° after drying overnight at 25° and 1 mm.

Anal. Calcd. for $C_{10}H_{12}N_2O_2 \cdot \frac{1}{2} H_2O$: C, 59.69; H, 6.51; N, 13.92. Found: C, 59.80, 59.52; H, 6.34, 6.42; N, 13.72, 13.79.

Tartaric Acid Salt of Metabolic (+)-Hydroxycotinine.—A solution containing 44 mg. of metabolic (+)-hydroxycotinine, m.p. 109.5–110.5°, obtained from the metabolism of (−)-cotinine in the human[7] and 36 mg. of (−)-tartaric acid in 0.5 ml. of methanol was treated with ether until a faint turbidity was produced and then was allowed to stand for several hours while a tartrate of (−)-hydroxycotinine precipitated. The salt, which was suitable for seeding, melted at 148–150°.

(+)-**Hydroxycotinine, Low-melting Isomer.**—A solution of 2.0 g. of (+, −)-hydroxycotinine, m.p. 70.5–72°, and 1.49 g. of (−)-tartaric acid in 10 ml. of methanol was diluted slowly with ether (approx. 5 ml.) until a slight turbidity persisted. The cloudy solution was seeded with a small crystal of the tartrate of metabolic hydroxycotinine (above). Scratching was continued until a crystalline fraction began to appear. The mixture was then allowed to stand overnight. The crystalline tartrate was collected and crystallized twice from methanol–ether, 750 mg., m.p. 140–142°. The salt was dissolved in ammonia water and extracted with chloroform as described for the resolution of the high-melting isomer (above). The residue from evaporation of the chloroform, m.p. 95–103°, was crystallized twice from ether–acetone to give 125 mg. of (+)-hydroxycotinine, m.p. 110–111°, which was dried for analysis at 28° and 1 mm.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.57. Found: C, 62.56; H, 6.36; N, 14.70. $[\alpha]^{28.5}_{D}$ +47.3° (*c*, 5.5 in methanol).

Upon admixture with a sample of metabolic hydroxycotinine,[7] m.p. 110–111°, $[\alpha]^{20}_{D}$ +49.2°, the melting point of the foregoing synthetic (+)-hydroxycotinine showed no depression.

[illegible] hydroxycotinine, m.p. 110–111°, was treated with methanolic picric acid. The yellow precipitate was recrystallized from methanol, m.p. 134.5–135.5°. The sample for analysis, which was dried at 25° and 1 mm., did not depress the melting point of the picrate of metabolic hydroxycotinine,[7] m.p. 134–136°.

Anal. Calcd. for $C_{16}H_{15}N_5O_9$: C, 45.61; H, 3.58; N, 16.62. Found: C, 45.78; H, 3.51; N, 16.61.

(+, −)-**Cotinine.**—A solution of 450 mg. of γ-(3-pyridyl)-γ-oxobutyric acid and 5 g. of methylamine was hydrogenated at 1 atm. and room temperature in the presence of 300 mg. of platinum on barium sulfate until approximately 1 equivalent of hydrogen had been taken up. After removal of the catalyst, the solution was evaporated to a clear gum (484 mg.). Upon paper chromatography in acidic system, the mixture showed a Koenig positive spot at R_f 0.27, corresponding in R_f value to authentic γ-(3-pyridyl)-γ-methylaminobutyric acid and another zone at R_f 0.33 corresponding to γ-(3-pyridyl)-γ-hydroxybutyric acid (obtained as a crude product from hydrogenation of γ-(3-pyridyl)-γ-oxobutyric acid as above but in the absence of methylamine). The gum was heated to 150–160° in an atmosphere of nitrogen for 10 min. The product was treated with chloroform–acetone (1–1 by vol.). An insoluble substance (79 mg.), R_f 0.33 (acid) was separated by filtration. The solution was placed upon a column of Florisil. An elution with acetone yielded an initial fraction which upon paper chromatography in the acid system showed a Koenig positive zone at R_f 0.38 and a subsequent fraction with Koenig positive material at R_f 0.38 and 0.42. The first fraction upon evaporation yielded 63 mg. of (+, −)-cotinine as an oil. Upon treatment with alcoholic picric acid the oil formed a yellow picrate which was recrystallized from methanol, m.p. 127–129°.

Anal. Calcd. for $C_{16}H_{15}N_5O_8$: C, 47.41; H, 3.73; N, 17.28. Found: C, 47.27; H, 3.96; N, 17.50.

(+, −)-**Chlorocotinine.**—(+, −)-Hydroxycotinine (isomer I), 340 mg., and 6 ml. of thionyl chloride were heated under reflux for 2 hr. The product, obtained by evaporation of the solvent, was dissolved in water and then placed on a column of Dowex 50 (H^+). The column was eluted with 0.1 *N* ammonia water, and the eluate was evaporated to obtain a crystalline residue, m.p. 115–123°. The analytical sample (305 mg.) was obtained by several recrystallizations from hexane–acetone, m.p. 132–135°, after drying at room temperature and 1 mm.

Anal. Calcd. for $C_{10}H_{11}N_2OCl$: C, 57.01; H, 5.26; N, 13.30. Found: C, 57.23; H, 5.04; N, 13.85.

(+, −)-**Cotinine from (+, −)-Chlorocotinine.**—A solution of 250 mg. of (+, −)-chlorocotinine (above) in 30 ml. of 95% ethanol containing 0.5 ml. of concentrated ammonia water was hydrogenated at atmospheric pressure in the presence of 300 mg. of 5% palladium on charcoal for 0.5 hr. After removal of the catalyst, the solvent was evaporated to obtain an oily residue (267 mg.), which cochromatographed with authentic (−)-cotinine in both the acidic and basic systems. The oil was dissolved in chloroform and placed on a column of Florisil. The column was eluted with acetone. The clear gummy residue (150 mg.) obtained from evaporation of the acetone was treated with an equivalent of picric acid (10% water) as a saturated solution in ethanol. The yellow crystalline picrate was recrystallized from ethanol and, after drying at room temperature and 1 mm., melted at 127–129°. The mixed melting point with an authentic sample of (+, −)-cotinine monopicrate (above) showed no depression.

Anal. Calcd. for $C_{16}H_{15}N_5O_8$: C, 47.41; H, 3.73; N, 17.28. Found: C, 46.93; H, 3.81; N, 17.35.

Chlorocotinine from Metabolic (+)-Hydroxycotinine.—A solution of 150 mg. of metabolic (+)-hydroxycotinine in 10 ml. of thionyl chloride was heated under reflux for 2 hr. The residue (153 mg.) from evaporation of the solvent was dissolved in water and placed upon a column (1 × 5 cm.) of Dowex 50 (H^+). After a water wash, the column was eluted with 0.1 *N* ammonia water. The residue from evaporation of the eluate was dissolved in 35–60° petroleum ether–acetone (1–1 by vol.). The cooled solution deposited colorless crystals, m.p. 108–110°, which showed a single Koenig positive zone at R_f 0.54 (acid) and R_f 0.74 (base). For analysis the sample was recrystallized from petroleum ether–acetone to a constant melting point of 112–114° which was unchanged upon drying at 60° over potassium hydroxide and 1 mm. for 8 hr.

Anal. Calcd. for $C_{10}H_{11}N_2OCl$: C, 57.01; H, 5.26; N, 13.30. Found: C, 57.20; H, 5.26; N, 13.10.

(−)-Cotinine from Metabolic (+)-Hydroxycotinine.—A solution of 645 mg. of chlorocotinine (obtained from metabolic (+)-hydroxycotinine) in 75 ml. of ethanol was hydrogenated at atmospheric pressure and room temperature in the presence of 350 mg. of 5% palladium on charcoal until 1 equivalent of hydrogen had been consumed. After removal of the catalyst, the solution was evaporated to dryness. A solution of the residue in ammonia water was extracted with chloroform. The chloroform solution was dried over sodium sulfate and then placed upon a column of alumina. The column was eluted with methanol to obtain 420 mg. of (−)-cotinine. To this was added 1 equivalent of picric acid in methanol. The crystalline monopicrate melted at 105–106° after recrystallization from methanol. The picrate was decomposed in dilute hydrochloric acid. After extraction of picric acid with ethyl acetate, the aqueous solution was adjusted to pH 10 with ammonia water and extracted with chloroform. The cotinine base from evaporation of the chloroform was treated with one equivalent of hydrobromic acid to give (−)-cotinine hydrobromide. The analytical sample was recrystallized from isopropyl alcohol and dried at 25° and 1 mm., m.p. 187–188° dec. $[\alpha]^{30}_{5461}$ −32.6°, (c, 7.4 in methanol).

Anal. Calcd. for $C_{10}H_{13}N_2OBr$: C, 46.71; H, 5.09; N, 10.90. Found: C, 46.65; H, 4.96; N, 10.92

The foregoing hydrobromide had a melting point and optical rotation in substantial agreement with the samples prepared[7] from metabolic and synthetic (−)-cotinine.

Isolation of Hydroxycotinine from Smokers' Urine.—Smoker's urine (60 l.) was obtained as voluntary daytime contributions from male laboratory workers, made alkaline, and then continuously extracted with chloroform as previously described.[7] The chloroform solution upon evaporation yielded a dark-brown oily residue (7.0 g.). The residue was treated with 40 ml. of boiling water, and the cooled mixture was filtered. The filtrate was adjusted to pH 2 with 5 *N* hydrochloric acid. The acidic solution was placed on a column of (4 × 30 cm.) of Dowex 50 (H^+). The column was washed thoroughly with water. Koenig positive material of R_f values 0.34, 0.61, 0.73, and 0.90 (base) was removed by exhaustive elution with 0.1 *N* ammonia water. The ammonical solution was placed upon a column (4 × 30 cm.) of Dowex 21K (OH^-). The ammoniacal effluent and exhaustive water wash were combined and concentrated to an oily residue (1.1 g.). The residue was dissolved in 20 ml. of chloroform and placed on a column of acid-washed alumina (30 g.). An elution with ether containing successively increasing amounts of methanol (0–100%, by vol.) served to remove a fraction with Koenig positive material, R_f 0.75 (base), which was identified as cotinine. Subsequent fractions contained material with R_f 0.61 (base) and the final fractions contained material showing a single Koenig positive zone at R_f 0.84 (base), which was cochromatographed with nicotine but was not identified as such. The combined R_f 0.61 fractions yielded upon evaporation an oily residue (118 mg.). The residue was treated with 1 ml. of dry pyridine and 1 ml. of acetic anhydride. After standing overnight at room temperature, the mixture was concentrated under diminished pressure. The oily residue (143 mg.) was dissolved in 5 ml. of chloroform and then placed upon a column of acid-washed alumina (5 g.). Elution with ether containing increasing amounts of methanol (0–100%) gave fraction A, which showed a single Koenig positive spot upon paper chromatography (R_f 0.75, base), and fraction B (R_f 0.61, base). The oil (17 mg.) from fraction B cochromatographed on paper with authentic crystalline (−)-demethylcotinine[8] in both acid and base. It failed to crystallize and was not identified. Fraction A was obtained as an oil (30 mg.). A sample (15 mg.) in 0.5 ml. of ethanol was treated with one equivalent of picric acid (15% water) as a saturated solution in ethanol. The resultant crystalline acetoxycotinine picrate (75 mg.) was recrystallized from ethanol, m.p. 165°. The analytical sample corresponded in melting point[17] to acetoxycotinine picrate which was obtained from studies on the dog.[5] Admixture produced no depression of the melting point. The two samples cochromatographed, R_f 0.77 (acid) and R_f 0.74 (base). For analysis the compound from smokers' urine was dried at 60° and 1 mm. over potassium hydroxide.

Anal. Calcd. for $C_{18}H_{17}N_5O_{10}$: C, 46.67; H, 3.70; N, 15.12. Found: C, 46.62; H, 3.74; N, 15.19.

Acknowledgment.—The authors wish to thank Mr. James E. Mann for his invaluable assistance and Dr. John Chemerda of Merck and Co. for supplies of alumina. Microanalyses were made by Spang Microanalytical Laboratory.

---

[17] This corrected capillary melting point was obtained at a heating rate of 0.30° per min. At approximately 140° a change in crystalline form was observed. At higher rates of heating the melting point is somewhat elevated (ref. 5).

A Comparison of Methods for the Preparation of 2- and 4-Styrylpyridines[1]

J. L. R. WILLIAMS, R. E. ADEL, J. M. CARLSON, G. A. REYNOLDS, D. G. BORDEN,
AND J. A. FORD, JR.

Kodak Research Laboratories, Eastman Kodak Company, Rochester, New York

Received August 27, 1962

Derivatives of 2-styrylpyridine, 5-ethyl-2-styrylpyridine, and 4-styrylpyridine bearing CH_3O, NO_2, CH_3, and $N(CH_3)_2$ in the 4′-position have been prepared by the following routes: 1) pyrolysis of the corresponding methiodides; (2) reaction of a benzaldehyde with a picoline in refluxing acetic anhydride; and (3) the zinc chloride condensation of a benzaldehyde and a picoline at 200°. A (2:5) mixture of *cis*- and *trans*-2-styrylpyridine was obtained from the reaction between a phosphorus ylid and 2-pyridylaldehyde. An analogous preparation gave *cis*-4-styrylpyridine from 4-pyridylaldehyde.

In preceding papers,[2] it was shown that the reaction of benzaldehyde with 2-picoline in refluxing acetic anhydride gave *trans*-2-styrylpyridine. Irradiation of *trans*-2-styrylpyridine, its hydrochloride or methiodide in solution with ultraviolet light gave the *cis* modification. In order to extend this study to include substituted and structurally isomeric styrylpyridines, it was necessary to examine various preparative methods for convenience, yields, and the isomer configurations obtained by these procedures.

Four methods were employed for the preparation of the styrylpyridines and are described in order as follows.

Method 1.—Phillips[3] prepared styrylpyridine methiodides by condensation of benzaldehydes with 2-picoline methiodide in methanol solution using piperidine as the catalyst. Horwitz[4] showed that the *trans* salts resulted when the same reaction was conducted using quinaldine methiodides in place of 2-picoline methiodide. On the basis of previous spectroscopic results from these laboratories,[2b] we have assigned the *trans* configuration to styrylpyridine methiodides prepared using piperidine as the catalyst. The physical properties of the styryl-

---

[1] Communication no. 2312 from the Kodak Research Laboratories, Eastman Kodak Co., Rochester, N. Y.

[2] (a) J. L. R. Williams, *J. Org. Chem.*, **25**, 1839 (1960). (b) J. L. R. Williams, S. K. Webster, and J. A. VanAllan, *ibid.*, **26**, 4893 (1961).

[3] A. P. Phillips, *ibid.*, **12**, 333 (1947).

[4] L. Horwitz, *J. Am. Chem. Soc.*, **77**, 1687 (1955).

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 238, No. 3, March 1963
Printed in U.S.A.

Studies on the Biological Activity of Nicotinylalanine, an Analogue of Kynurenine*

R. H. DECKER,† R. R. BROWN,‡ AND J. M. PRICE§

From the Cancer Research Division, Department of Surgery, University of Wisconsin Medical School, Madison 6, Wisconsin

(Received for publication, November [illegible], 1962)

Considerable evidence has been obtained that 3-hydroxyanthranilic acid and quinolinic acid can be converted to niacin in the intact rat (2–9). The usually low yield of niacin from these compounds suggested that another pathway from tryptophan to niacin might exist. Thus, kynurenine or hydroxykynurenine might be converted to niacin through an intermediate such as γ-(3-pyridyl)-γ-oxo-α-aminobutyrate (referred to as nicotinylalanine) via ring oxidation and rearrangement similar to that known to occur with 3-hydroxyanthranilic acid (Fig. 1). To test this hypothesis, nicotinylalanine was synthesized and tested as a possible precursor of niacin in the intact rat and in tissue preparations.

Nicotinylalanine is relatively nontoxic, and its intraperitoneal injection was followed by an increase in urinary excretion of *N*-methylnicotinamide. When nicotinylalanine was incubated with rat liver homogenates, it appeared to be converted to nicotinic acid by a kynureninase-like enzyme. In studies with tryptophan-3-C^{14}, data were obtained indicating that nicotinylalanine is not an intermediate in the conversion of tryptophan to niacin. However, it was found that nicotinylalanine is an effective inhibitor of kynureninase and kynurenine hydroxylase *in vivo* and *in vitro*.

EXPERIMENTAL PROCEDURE

Reagents—DL-Tryptophan-3-C^{14} of specific activity of 3.74 mc per mmole was obtained from New England Nuclear Corporation. Diethyl-γ-(3-pyridyl)-γ-oxo-α-acetamido-α-carbethoxybutyrate,[1] which was used as an intermediate in the synthesis of hydroxycotinine by Turnbull, Bowman, and McKennis (10) was refluxed in 6 N HCl for 6 hours to convert it to nicotinylalanine, which was crystallized as the sulfate from 80% ethanol (m.p. 204°, uncorrected).

$C_9H_{12}O_7N_2S$

Calculated	C 36.99,	H 4.14	O 38.32	N 9.59,	S 10.97
Found[2]	C 36.86	H 4.30	O 38.51	N 9.24	S 11.29

Animals—Male albino rats weighing 150 to 200 g were fed a purified diet (11) and housed in stainless steel metabolism cages. Urine was collected in flasks containing 0.15 ml of xylene and 0.15 ml of glacial acetic acid for each 24-hour volume. Tryptophan and nicotinylalanine were administered by intraperitoneal injection of an aqueous solution. Nicotinylalanine usually was administered free of sulfate ion, which was precipitated by the addition of an equivalent of powdered barium carbonate to an aqueous solution of the compound.

Excretion of N-Methylnicotinamide after Injection of Tryptophan and Nicotinylalanine—L-Tryptophan, nicotinylalanine, or both were injected into groups of four rats (2.5 μmoles per g of body weight). Urine was collected from the animals for 24 hours before and after injection of the supplements. Samples of urine equivalent to approximately 3% of a 24-hour collection from one rat were used to determine *N*-methylnicotinamide by the procedure of Vivian, Reynolds, and Price.[3]

Incubation of Nicotinylalanine with Rat Liver Preparations—Nicotinylalanine was incubated with a 20% rat liver homogenate prepared in 0.9% sodium chloride with a Potter-Elvehjem homogenizer. The reaction mixtures contained 2 ml of the homogenate, 5 μmoles of nicotinylalanine, 40 μg of pyridoxal phosphate, and 0.[illegible] ml of 1.5 M phosphate buffer at pH 7.2 in a 3-ml final volume. Controls contained 5 μmoles of L-kynurenine in place of the nicotinylalanine. Incubation was carried out at 37°, and reactions were stopped by addition of 1 ml of 1 N trichloroacetic acid at the times indicated in Fig. 3. The clear supernatant solutions were diluted to 15 ml and placed on Dowex 50W columns, 1 × 11 cm. The columns were washed with 50 ml of 1 N HCl, and the nicotinic acid was eluted with 120 ml of 2.4 N HCl. The eluates were taken to dryness on a rotary evaporator before neutralization and removal of the aliquots for microbiological assay of nicotinic acid with *Lactobacillus plantarum* (12) (formerly named *L. arabinosus*). The extent of growth was determined by measurement of turbidity at 650 mμ.

Influence of Nicotinylalanine on Nicotinamide Adenine Dinucleotide Levels in Rat Liver[4]—Nicotinylalanine sulfate was

---

* Supported in part by grants from the American Cancer Society and the National Institutes of Health (A-1499 and C-3274), United States Public Health Service. A preliminary report of this work has been presented at the Federation of American Societies for Experimental Biology Meetings in Atlantic City, 1962 (1).

† Postdoctoral fellow (CPD-13,291 [illegible]) of the National Cancer Institute.

‡ Recipient of a Research Career Development Award (CA-K3-18,404) of the National Institutes of Health, United States Public Health Service.

§ American Cancer Society-Charles S. Hayden Foundation Professor of Surgery in Cancer Research.

[1] Additional details concerning the synthesis of this compound were kindly provided in personal communications from Dr. H. McKennis, Jr.

[2] Elemental analyses were made by Huffmann Microanalytical Laboratories, Wheatridge, Colorado.

[3] V. M. Vivian, M. S. Reynolds, and J. M. Price, unpublished observations.

[4] These data were kindly provided by Dr. Frederick N. Minard

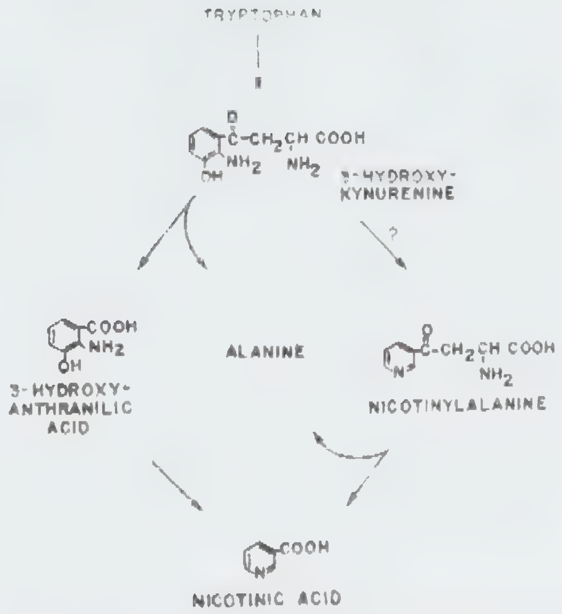


Fig. 1. The main pathway of tryptophan degradation, showing the location of the postulated intermediate, nicotinylalanine.

administered at the level of 0.27 μmole per g of body weight to seven rats 1 to 4 hours before death. The NAD in the liver was extracted from the frozen tissue with perchloric acid and determined by the method of Jedeikin and Weinhouse (13).

Metabolism of DL-*Tryptophan-3-C^{14} in Presence of Nicotinylalanine in Vivo*—The method of Weinhouse and Friedmann (14) was employed in the metabolite overloading experiment with nicotinylalanine. DL-Tryptophan-3-C^{14} (3.9 μmoles; 14.6 μc) was administered to each of two 170-g rats. One rat also received 0.9 mmole of nicotinylalanine in addition to the labeled tryptophan, and the urine was collected from the animals for 12 hours. Carrier kynurenine and nicotinylalanine were added to the urines and were separated by gradient elution from a Dowex 50W column, 15 × 1.5 cm, with HCl. Kynurenine and nicotinylalanine were recrystallized to constant specific activity from ethanol as the sulfate salts before the radioactivity was counted. The C^{14} content of solid samples was determined with a Nuclear-Chicago thin window gas flow counter.

Assays of Enzymes Involved in Tryptophan Metabolism—Tryptophan pyrrolase, kynureninase, kynurenine hydroxylase, and kynurenine transaminase were determined in rat liver preparations by the method of DeCastro, Brown, and Price (15). Nicotinylalanine, 10 μmoles (twice the substrate concentration), was added to determine its effect on the enzyme activity. Incubations were carried out at 37° for 1 hour.

The effect of nicotinylalanine on the adaptation of hepatic tryptophan pyrrolase was determined in two experiments. In the first study, nicotinylalanine sulfate was administered intraperitoneally to a group of four rats at a dose of 2.5 μmoles per g of body weight 3 hours before death and assay of enzyme activity. A second group of four animals received, per g of body weight, 2.5 μmoles of L-tryptophan and 2.5 μmoles of nicotinylalanine. Control groups of animals were given either L-tryptophan at this level (four rats) or NaCl solution (three rats). The second study was the same in design, but groups of five rats were given 7.5 μmoles of nicotinylalanine (with the sulfate removed by $BaCO_3$ treatment) and 5.0 μmoles of L-tryptophan per g of body weight. The compounds were neutralized and suspended or dissolved in 2.0 ml of NaCl solution before administration.

Influence of Nicotinylalanine on Urinary Excretion of Tryptophan Metabolites—Loading doses of L-tryptophan (2.5 μmoles per g of body weight) were given to two groups of five rats; one group also received 2.5 μmoles of nicotinylalanine per g of body weight. Urine was collected from each group for 24 hours. Samples of rat urine equivalent to approximately 50% of a 24-hour collection from one rat were resolved into five fractions on columns of Dowex 50W by the method of Brown and Price (16) for the determination of the diazotizable aromatic amines with a modified procedure of Bratton and Marshall (16, 17). 3-Hydroxykynurenine was determined as described by Brown (18). Kynurenic and xanthurenic acids were determined by the method of Satoh and Price (19). 3-Hydroxyanthranilic acid was isolated and measured by the method of Pamukcu, Brown, and Price (20).

RESULTS

Excretion of N-Methylnicotinamide after Injection of Tryptophan and Nicotinylalanine—The data in Fig. 2 are the average of four studies. Administration of DL-nicotinylalanine and L-tryptophan separately produced 4-fold increases in the urinary excretion of *N*-methylnicotinamide over the basal level. Simultaneous administration of the two compounds revealed that they were not additive in their effects on the urinary excretion of *N*-methylnicotinamide.

Conversion of Nicotinylalanine to Nicotinic Acid by Rat Liver Preparations—Incubation of nicotinylalanine with the rat liver homogenates resulted in a linear increase in nicotinic acid activity for *L. plantarum* (Fig. 3). The liver preparations catalyzed this reaction at a rate of 0.45 μmole per g of tissue, wet weight, per hour. The control reaction mixture containing kynurenine produced an insignificant increase in niacin activity. Nicotinylalanine itself was inactive as a source of niacin in the microbiological assay and did not inhibit the bacterial utilization of nicotinic acid.

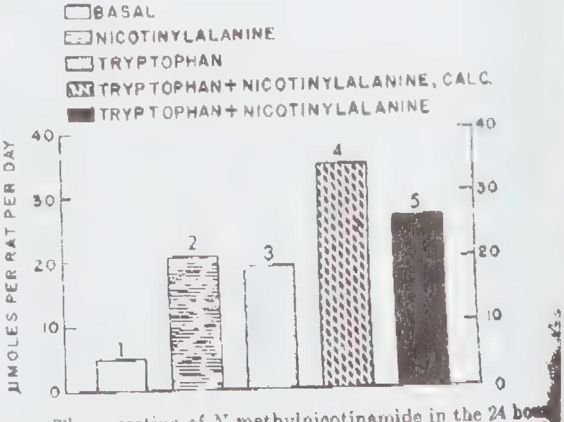


Fig. 2. The excretion of *N*-methylnicotinamide in the 24 bo after the injection of tryptophan, nicotinylalanine, or bo *TRYPTOPHAN + NICOTINYLALANINE, CALC* is the of *Bars 2 and 3* minus *Bar 1*, or the calculated yield of *N*-met nicotinamide

---

of the Biochemical Research Department, Abbott Laboratories, North Chicago, Illinois

nfluence of Nicotinylalanine on NAD Levels in Rat Liver—otinylalanine produced a 20% increase in NAD levels of liver over a period of 1 to 4 hours after administration of 7 µmole of the compound per g of body weight. The mean ue of the controls was 0.79 ± 0.020 µmole per g of liver, weight, whereas the mean of the test group was 0.94 ± 0.024. e two means were significantly different ($p < 0.001$).

Metabolism of DL*-Tryptophan-3-*C^{14} *in Presence of Nicotinyl-nine in Vivo*—The injected nicotinylalanine was intended to as an overloading dose that would be excreted in the urine h compound labeled from tryptophan, if present. The ioactivities of the kynurenine and nicotinylalanine isolated m the urine of the two rats are shown in Table I. A small ount of radioactivity appeared in the nicotinylalanine fraction both experiments, but a second chromatographic separation wed that the isotope peak did not correspond with the peak the compound and was an impurity. Kynurenine radio ivity was increased 5.5 times when the rat was given nicotinyl-nine with the labeled tryptophan.

Effect of Nicotinylalanine on Enzymes Involved in Tryptophan etabolism—Table II shows typical data obtained when nico-ylalanine was incubated in the assays of four enzymes involved the first stages of tryptophan degradation. The compound did t influence the activities of tryptophan pyrrolase or kynurenine nsaminase, but kynureninase and kynurenine hydroxylase re inhibited 63 and 53%, respectively, in the presence of a bstrate to inhibitor ratio of 1:2. Nicotinylalanine had no ect on the NADPH-generating system of the hydroxylating action. Inhibition could be reversed in both the kynureninase d hydroxylase reactions by increasing the substrate concentra-on.

The data in Table III indicate that administration of nicotinyl-anine sulfate produced a 2-fold increase in the activity of liver yptophan pyrrolase compared with the controls that received aCl solution, whereas L-tryptophan at the same concentration sulted in a 4-fold increase in enzyme activity. When both yptophan and nicotinylalanine were injected there was a small crease in pyrrolase activity as compared with the effect pro-uced by tryptophan alone. However, nicotinylalanine admin-stered free from the sulfate ion (Table III) did not show a signifi-ant effect on tryptophan pyrrolase, even when the dose was 3 imes that used in the first experiment.

Influence of Nicotinylalanine on Urinary Excretion of Trypto-phan Metabolites—Nicotinylalanine produced marked changes in the urinary excretion of some tryptophan metabolites. The results in Fig. 4 are from one of four experiments of this type. Considerable variation was observed from one experiment to another in the levels of urinary metabolites excreted, depending upon animal size and dosages given, but the qualitative results were much the same. Although moderate increases were observed in anthranilic acid glucuronide, *o*-aminohippurate, kynurenine, and hydroxykynurenine, the greatest increases were noted with *N*-methylnicotinamide, kynurenic acid, and xanthurenic acid. That the apparent change in kynurenic and xanthurenic acid levels was not the result of interference in the assay by metabolites of nicotinylalanine was shown by measuring these tryptophan metabolites in the 24-hour urines from rats

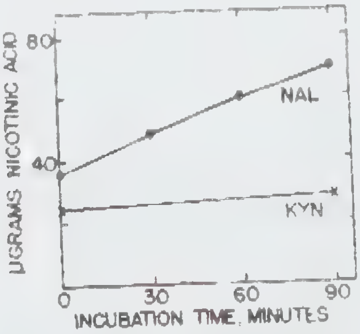


FIG. 3. The formation of nicotinic acid from nicotinylalanine by a rat liver homogenate. Abbreviations used are: *NAL*, nicotinylalanine, *KYN*, kynurenine.

TABLE I

Radioactivity of kynurenine and nicotinylalanine in 12-hour rat urines after injection of DL*-tryptophan-3-*C^{14} *with and without nicotinylalanine*

Administered	Total radioactivity		
	Kynurenine	Nicotinylalanine	Urine
		mµc	
Tryptophan-3-C^{14}	11.49	0.11	495.0
Tryptophan-3-C^{14} + nicotinylalanine	64.35	0.09	2160.0

TABLE II

Effect of nicotinylalanine on activity of enzymes involved in tryptophan metabolism

Enzyme	Activity*		Inhibition
	Control	Nicotinylalanine	
			%
Tryptophan pyrrolase	3.08	3.08	
Kynureninase	3.24	1.19	63
Kynurenine transaminase	3.31	3.32	
Kynurenine hydroxylase	1.74	0.82	53

* Activity is expressed as micromoles of product formed per g of fresh liver, wet weight, per hour.

TABLE III

Effect of nicotinylalanine on hepatic tryptophan pyrrolase adaptation

Administered	Kynurenine produced	
	Experiment A*	Experiment B†
	µmoles/g/hr	
NaCl solution	0.82	2.05
Nicotinylalanine	1.81	2.21
Tryptophan	3.09	6.68
Tryptophan + nicotinylalanine	3.45	6.01

* Nicotinylalanine as the sulfate salt was given intraperitoneally at 2.5 µmoles per g of body weight, and tryptophan, at 2.5 µmoles per g of body weight.

† Nicotinylalanine free of sulfate was given at 7.5 µmoles per g of body weight, and tryptophan, at 5.0 µmoles per g of body weight.

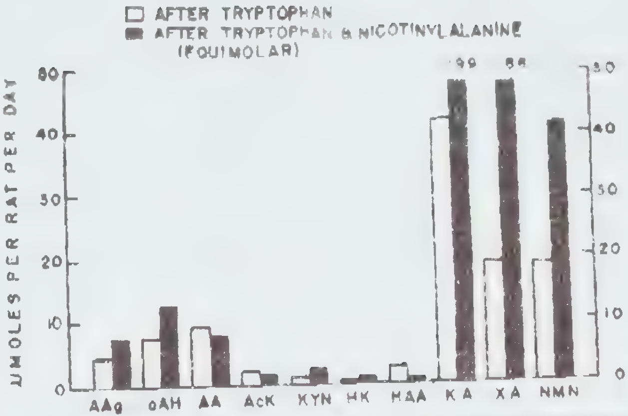


Fig. 4. Levels of urinary excretion of tryptophan metabolites in the 24 hours after the injection of tryptophan with and without nicotinylalanine. The following abbreviations are used: *AAg*, anthranilic acid glucuronide; *oAH*, o-aminohippuric acid; *AcK*, acetylkynurenine; *KYN*, kynurenine; *HK*, hydroxykynurenine; *HAA*, hydroxyanthranilic acid; *KA*, kynurenic acid; *XA*, xanthurenic acid; *NMN*, *N*-methylnicotinamide.

with only nicotinylalanine. Kynurenic acid and xanthurenic acid accounted for 88% of the total increase in the metabolites measured. 3-Hydroxyanthranilic acid excretion was not appreciably increased when nicotinylalanine was administered with tryptophan.

DISCUSSION

Since *N*-methylnicotinamide is a major urinary metabolite of niacinamide in the rat (21), the level of its excretion was used as a guide to niacin production *in vivo*. DL-Nicotinylalanine was approximately as effective as L-tryptophan in increasing the excretion of *N*-methylnicotinamide. If only the L-isomer of nicotinylalanine was utilized, as is the case with tryptophan (22), it appears that the compound was twice as efficient as tryptophan as a source of niacin. The formation of nicotinic acid from nicotinylalanine by a liver enzyme seems likely to have occurred by a hydrolytic reaction much like that catalyzed by kynureninase. In view of the limited specificity of the enzyme (23), such a reaction is not surprising.

The rise in the NAD levels of the rat livers provided further evidence that nicotinylalanine was converted to niacin *in vivo*. Although neither experiment ruled out the apparent production of *N*-methylnicotinamide or NAD by altering metabolism of nicotinylalanine, the fact that nicotinic acid was produced *in vitro* gives strong support to the possibility that it was formed *in vivo* as well.

Although these experiments established that nicotinylalanine could give rise to niacin, they did not prove that nicotinylalanine is a metabolite of tryptophan in the rat. Observations made with labeled tryptophan did not support its role as an intermediate, since no radioactive nicotinylalanine could be detected in the urine after injection of tryptophan-C^{14} either with or without loading doses of nicotinylalanine. The analogue functioned in a different manner, however, causing an increased excretion of labeled kynurenine and other radioactivity in the urine. Because of the similarities in structure between kynurenine and nicotinylalanine, a logical explanation was that the latter inhibited metabolism of kynurenine to niacin. This would explain why the administration of tryptophan and nicotinylalanine did not cause an additive increase in *N*-methylnicotinamide excretion. Both kynureninase and kynurenine hydroxylase were inhibited by nicotinylalanine *in vitro*. Since hydroxykynureninase and kynureninase are presumably the same enzyme (23), a "sequential block" (24) in the pathway would result if this occurred *in vivo*. The increased accumulation of kynurenine metabolites in urine after tryptophan was given with nicotinylalanine supported the conclusion that inhibition of these enzymes occurred *in vivo* as well. The possibility that the increase in metabolite excretion was caused by tryptophan pyrrolase adaptation, which resulted in more kynurenine being produced, was ruled out when it was found that nicotinylalanine and tryptophan injection did not increase induction of enzyme activity appreciably over the level obtained when tryptophan was given alone. The 2-fold adaptation caused by nicotinylalanine sulfate (Table III) probably was caused by the stress arising from the salts accompanying the compound (25), since this adaptation did not occur in a similar experiment (Table III) when the sulfate was removed, even when the dose of nicotinylalanine was increased 3-fold.

Results of the quantitative determination of several tryptophan metabolites in the urine are not easily interpreted, since both kynurenine and inhibitor concentrations probably were in a fluctuating state. Kynurenine and kynurenic acid were expected to accumulate when kynurenine hydroxylase and kynureninase would be inhibited. Inhibition of hydroxykynureninase would also result in an increased excretion of hydroxykynurenine and xanthurenic acid. Xanthurenic acid and kynurenic acid accounted for more than 85% of the total increase in the tryptophan metabolites measured in nearly all experiments. The observation that nicotinylalanine produced only moderate increases in urinary kynurenine and hydroxykynurenine would be expected if the excess of these metabolites were adequately shunted to the accelerated transaminase reactions effecting an increase in the production of kynurenic and xanthurenic acids.

Although the anthranilic acid conjugates, o-aminohippuric acid and anthranilic acid glucuronide, are products of the kynureninase reaction, their excretion was increased when nicotinylalanine was administered with tryptophan. The accumulation of kynurenine resulting from the sequential block would tend to shift the equilibrium of the kynureninase reaction in favor of anthranilic acid. The decreased urinary level of 3-hydroxyanthranilic acid, the product of hydroxykynureninase, is consistent with the evidence for a sequential block.

SUMMARY

Intraperitoneal administration of nicotinylalanine to rats caused a 4-fold increase in urinary *N*-methylnicotinamide, and incubation of nicotinylalanine with rat liver homogenates produced a linear increase in nicotinic acid with time. Data obtained in isotope carrier and "overloading" studies with tryp phan-3-C^{14} indicated that nicotinylalanine is not a metabo of tryptophan; instead, it acted as an antimetabolite of ky renine by inhibiting kynureninase and kynurenine hydroxy *in vitro*. Evidence was obtained to indicate that inhibi occurred *in vivo* as well, resulting in a sequential block of major route of kynurenine degradation.

Acknowledgment—The authors wish to acknowledge the technical assistance of Miss Margaret Kowitz in these stu

REFERENCES

DECKER, R. H., AND BROWN, R. R. *Federation Proc.*, **21** 3 (1962).

HENDERSON, L. M., *J. Biol. Chem.* **181** 77 (1949).

HANKES, L. V., AND SEGEL, I. H. *Proc. Soc. Exptl. Biol. Med.*, **96**, 447 (1957).

MITCHELL, H. K., NYC, J. F., AND OWEN, R. D., *J. Biol. Chem.*, **175**, 433 (1948).

WISS, O., VIOLLIER, G., AND MULLER, M. *Helv. Physiol. et Pharmacol. Acta*, **7**, C 64 (1949).

LBERT, P. W., SCHEER, B. T., AND DEUEL, H. J., JR., *J. Biol. Chem.*, **175**, 479 (1948).

HANKES, L. V., AND HENDERSON, L. M., *J. Biol. Chem.*, **225**, 349 (1957).

HANKES, L. V., AND URIVETSKY, M. *Arch. Biochem. Biophys.*, **52**, 484 (1954).

LLINGER, P., FRAENKEL, G., AND ABDEL KADER, M. M., *Biochem. J.*, **41**, 559 (1947).

RNBULL, L. B., BOWMAN, E. R., AND MCKENNIS, H., JR., *Abstracts of the 135th meeting of the American Chemical Society, April, Boston, 1959*, p. 59C.

BROWN, R. R., MILLER, J. A., AND MILLER, E. C., *J. Biol. Chem.*, **209**, 211 (1954).

12. SNELL, E. E., AND WRIGHT, L. D. *J. Biol. Chem.*, **139**, 675 (1941).
13. JEGEIKIN, L. A., AND WEINHOUSE, S., *J. Biol. Chem.*, **213**, 271 (1955).
14. WEINHOUSE, S., AND FRIEDMANN, B., *J. Biol. Chem.*, **197**, 733 (1952).
15. DECASTRO, F. T., BROWN, R. R., AND PRICE, J. M., *J. Biol. Chem.*, **228**, 777 (1957).
16. BROWN, R. R., AND PRICE, J. M., *J. Biol. Chem.*, **219**, 985 (1956).
17. BRATTON, A. C., AND MARSHALL, E. K., JR., *J. Biol. Chem.* **128**, 537 (1939).
18. BROWN, R. R., *J. Biol. Chem.*, **227**, 649 (1957).
19. SATOH, K., AND PRICE, J. M., *J. Biol. Chem.*, **230**, 781 (1958).
20. PAMUKCU, A. M., BROWN, R. R., AND PRICE, J. M., *Zentr. Veterinarmed.*, **6**, 361 (1959).
21. LIN, P. H., AND JOHNSON, B. C., *J. Am. Chem. Soc.*, **75**, 2974 (1953).
22. HENDERSON, L. M., KOSKI, R. E., AND D'ANGELI, F., *J. Biol. Chem.*, **215**, 369 (1955).
23. WISS, O., AND FUCHS, H., *Experientia*, **6**, 472 (1950).
24. POTTER, V. R., *Proc. Soc. Exptl. Biol. Med.*, **76**, 41 (1951).
25. KNOX, W. E., AND MEHLER, A. H., *Science*, **113**, 237 (1951).

Sacramento City College
Serving the Future Since 1916

26 August 1994

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

Dear Dr. Bader,

Please excuse my long delay in responding to your kind note; I was in the process of finishing my manuscript for the Meitner biography and wasn't doing anything else.

I don't think *Chemistry in Britain* offered reprints; in any event, I don't have any. So I'm enclosing an ordinary copy, and also a reprint from an article in *Angewandte Chemie* that I hope you will enjoy.

With best wishes,

Sincerely yours,

Ruth Sime

Dr. Ruth Lewin Sime
Department of Chemistry

3835 Freeport Boulevard, Sacramento, CA 95822-1386
Los Rios Community College District
The Los Rios Community College District is an affirmative action equal opportunity organization

Ruth Sime

A split decision?

Fifty years ago, Otto Hahn took the limelight for discovering nuclear fission, while Lise Meitner was shunted aside. However, despite the fact that she was excluded from the Nobel prize, her work towards fission was equally important.

Half a century ago, towards the end of a terrible war, when nuclear weapons were being built in secret but the bomb was not yet a reality, Otto Hahn was awarded the 1944 Nobel prize for chemistry. The Swedish Royal Academy of Sciences cited him for his life's work in radiochemistry and the discovery of nuclear fission.

Hahn may well have been the world's foremost radiochemist, but he did not discover fission by himself, and radiochemistry was just one of several disciplines essential to the discovery. Two other scientists, whose work played a fundamental part, were omitted from the award. One of these was Fritz Strassmann, a young chemist whose analytical expertise had been crucial; the other was Lise Meitner, the physicist who led their Berlin team, provided the fundamental physical context for their work, and gave the first theoretical interpretation of the fission process. While Strassmann's omission may exemplify the Nobel committee's tilt towards established scientists, Meitner's exclusion reflects the twisted history of the time. The Nazi racial persecution forced her to flee Berlin just before the discovery, and her poor professional status as a refugee in Sweden inhibited proper assessment of her work and kept her from a Nobel prize.

In the shadow

Such is the prestige of a Nobel award that a questionable or mistaken decision can skew the history of a discovery, and obscure the contributions of those left out. This was particularly true for the nuclear fission discovery and Hahn's award. As nuclear fission captured the world's attention and Hahn became a post-war scientific celebrity, Strassman remained 'in the shadow of the sensation'—as his biographer aptly put it[1]—and Meitner and physics were shunted aside. One writer has sardonically described[2] Meitner's work as being 'crowned by the Nobel prize for Otto Hahn'. This statement may be a simplification, but it is not an exaggeration.

Joining forces

In a complex story such as this, it is well to begin with the science. The scientific literature clearly shows that the discovery of nuclear fission relied on an essential interplay between physics and chemistry. Such interdisciplinary collaboration had been Meitner and Hahn's forte from the time they met in Berlin in 1907. Both were then 28 years old—Lise was fresh from her physics doctorate in Vienna, and Otto was a promising young chemist. Together, they made their mark in radioactivity, discovering protactinium in 1918, while working at the Kaiser Wilhelm Institute for Chemistry in Berlin-Dahlem. In the 1920s they worked separately—Hahn refined radiochemical techniques, while Meitner pioneered the new field of nuclear physics. She became one of the most prominent physicists of her day, receiving many awards, and was repeatedly nominated for a Nobel prize.[3] During that time, Hahn later noted, it was her work, more than his, that brought international recognition to their institute.[4] It was nuclear physics, more than radiochemistry, that charted the 'uranium project' they would soon begin.

In 1934, when Enrico Fermi began irradiating elements with neutrons to produce artificial radioactivities, Meitner immediately repeated and verified his experiments. When Fermi irradiated uranium and found several new activities, he suggested the possibility of elements beyond uranium. Meitner was fascinated, and asked Hahn to join her for their first collaboration in many years, but it took her several weeks to get him interested.[5] Strassmann joined them a few months later, and the Berlin team pursued the uranium project for the next four years. The investigation was fuelled by chemical data, but directed and interpreted by nuclear physics. As the chemists disentangled more activities, they confidently reported the 'transuranes' as 'unquestionable', there being 'no doubt' that these were elements beyond uranium. However, the physical interpretation buckled under the profusion of 'transuranes'. It was Meitner's task to integrate the chemistry, radiochemistry, and the physical measurements she had made, into nuclear reactions that made sense. Her recognition that the nuclear reactions devised for 'transuranes' were inconsistent with known nuclear behaviour kept the investigation going, until it was later recognised that 'transuranes' were fission fragments.

Hahn later blamed physics for the mistakes in interpretation that delayed the discovery, in an attempt to claim fission for chemistry—and himself—alone. Physics did not predict fission, but it detected errors that chemistry could not. Without physics, chemists would not have begun the investigation; without physics they would have had no reason to sustain it.

In the autumn of 1938, after Irène Curie and Paul Savitch in Paris reported a strong new activity, the Berlin chemists found

that it followed a barium carrier and therefore attributed it to radium. Meitner objected vehemently on theoretical grounds—radium could not possibly result from the slow neutron irradiation of uranium. The chemists looked again, and found that it was not radium, but barium: the uranium nucleus had split. Within days, Meitner and her physicist nephew, Otto Robert Frisch, interpreted the process. Likening the nucleus to an unstable liquid drop, they calculated the energy released and explained the false 'transuranes' as fission fragments.[6] The first physical verification came when Frisch detected huge pulses from fission fragments in an ionisation chamber.[7]

Taken as a whole, we can see that the fission discovery was an interdisciplinary achievement—it relied on data from analytical and radiochemistry, but was initiated, framed, driven and ultimately interpreted by nuclear physics. Other scientists contributed much and came very close, but the success of the Berlin team surprised no one, so unique—and so essential—was their collective expertise.[8]

Frisch (*left*, Meitner's nephew, a fellow of Trinity College, Cambridge), Meitner, and Max Born (*right*, a physicist at the University of Edinburgh) in Cambridge, *ca* 1950.

Exile and exclusion

Had the Nazis never existed, this would have been the undisputed history of the discovery of fission. But Meitner was of Jewish origin, and she had fled Germany in July 1938, just five months before the barium finding.[9] By September 1938, she was in Stockholm, but still a *de facto* member of the Berlin team. She and Hahn corresponded constantly; they met in Copenhagen in November 1938—secretly, three days after *Kristallnacht**—and it was there that Meitner urged Hahn to examine their 'radium' findings more rigorously than before.[10] Her objections were the impetus for the experiments that led directly to the detection of barium as a fission product a few weeks later. In a letter to Meitner on 19 December 1938, Hahn described† barium as a 'frightful result' and begged her for some 'fantastic explanation... if you could publish, it would still in a way be work by the three of us!'[11] Strassmann, too, believed that Meitner still 'belonged to our team'—but German racial policies made it impossible for her to publish with them. The barium report, under the names of Hahn and Strassmann only, appeared in *Naturwissenschaften* on 6 January 1939.[12]

Meitner and Hahn in their laboratory, at the Kaiser Wilhelm Institute for Chemistry, Berlin-Dahlem, *ca* 1920, shortly after their discovery of protactinium.

Meitner and Frisch did explain the fission process and they did publish it, in *Nature*, on 11 February 1939.[13] Their interpretation had immediate and wide impact. Niels Bohr used it as a starting point for further nuclear theory, and also relied on physical measurements done by Meitner in 1937 to deduce that ^{235}U—but not ^{238}U—is fissile with slow neutrons.[14]

However, to Hahn the discovery was no longer 'work by the three of us.' As a non-Nazi he was vulnerable: he found it difficult to acknowledge his ongoing collaboration with a 'non-Aryan' in exile, or even the value of her earlier contributions. By February 1939, he had convinced himself that fission had nothing to do with Meitner and physics: 'In all our work [Strassmann and I] absolutely did not touch upon physics but instead we did chemical separations over and over again' he wrote to Meitner. He described the discovery as a 'gift from heaven' that would protect him and his institute from political interference,[15] but this was a self-deception, brought on by fear.

Meitner realised that those who did not understand her work or the political situation would not know that she had been unjustly excluded from the discovery. Unfortunately, this was the case in her new host country. Not only was Sweden exceedingly weak in experimental nuclear physics, so that Meitner's expertise was neither recognised nor appreciated, but it

---

*Also known as the 'night of broken glass', on the night of 9 November 1938, when the government incited a huge pogrom resulting in the burning of synagogues and the killing or imprisonment of many Jews all across Germany

†Hahn considered the barium a 'frightful result' because in all of their previous work they had supposed that irradiating uranium with neutrons would produce only small nuclear changes, *ie* elements near uranium

lacked an immigrant tradition and maintained strong cultural ties to Germany well into World War II so there was no particular sympathy for Jewish refugees.

Meitner had taken a position in Manne Siegbahn's new Nobel Institute for Experimental Physics but this had turned out badly. For whatever reason—conflicting personalities, resentment of a prominent outsider, gender bias—she was marginalised from the start, neither taken into Siegbahn's group nor given the resources to form her own. Siegbahn, a Nobel laureate, was a major force in Swedish physics, influential in the Royal Academy of Sciences and a member of the Nobel physics committee.

A hasty decision

When the Nobel chemistry prize was awarded to Hahn in 1944, it was not announced because Germans under Hitler were forbidden to accept Nobel awards. The decision must have been hasty, however, because in 1945 the chemistry section of the Royal Academy took the highly unusual step of reconsidering its 1944 award to evaluate the contributions of others, in particular Meitner and Frisch. After much debate, a slim majority of the entire academy voted to retain its original decision. At the same time, Meitner and Frisch were nominated for the physics prize, to no avail. Meitner's friends were sure Siegbahn was behind it—and that he represented a 'dangerous obstacle' to her ever receiving an award for physics.[16]

The timing of Hahn's award—so soon after Hiroshima and Nagasaki—commanded exceptional attention, placing Hahn in the limelight, Strassmann in his shadow, and Meitner nearly invisible in the wings. In Germany, Hahn was made into a virtual icon: a great scientist, a man who withstood the Nazis, a decent German. But Hahn's treatment of his once closest colleague and best friend was anything but decent—he did all he could to exclude Lise Meitner from the fission discovery. In his numerous memoirs and autobiographies he gave no sense of their early work together, and did not mention her initiative in 1934, her leadership of their team, their ongoing collaboration after she left Berlin, or their crucial meeting in Copenhagen. Fission, he always insisted, was made in opposition to the ideas of physics.

In part, this may be a turf dispute between chemists and physicists, but most of it was political. Hahn was a nationalist, who hated the Nazis, but loved Germany; he wanted to use the importance of fission and the prestige of his Nobel award to rebuild German science and repair Germany's moral standing. For this he wanted the discovery to be his, and his alone. He saw no purpose in looking back to the injustices of the Nazi period; he felt no personal necessity to make amends. 'He suppresses the past with all his might,' Meitner observed in 1947; 'I am part of that suppressed past'.[17] Hahn's behaviour typified the willed historical amnesia that prevailed in Germany after the war.

In 1960 Meitner moved from Stockholm to Cambridge, to be near to Frisch and his family. It was there in 1968, at the age of 90, that she died.

Changing history

In the years that followed, Meitner's name hovered at the periphery, barely acknowledged for the discovery itself; usually credited for her work with Frisch; sometimes entirely missing, as in the *Deutsches Museum* in Munich. For over 30 years—until corrected in 1991—it displayed her physical apparatus under the sign '*Werktisch* [worktable] *von Otto Hahn*' without mentioning her name at all. Meitner is often described as Hahn's *Mitarbeiterin* [co-worker], his assistant, even his student, which was gender bias pure and simple: woman-as-subordinate. It also represents a failure for science historians: for a generation after the Nobel award, almost no one saw fit actually to examine the record. However, the record exists—in the scientific literature, personal correspondence, even the Nobel archives that will soon open after 50 years. Most importantly, a new generation—as much in Germany as elsewhere—is ready to explore the troubled history of that time.

Dr Ruth Sime can be contacted at the department of chemistry, Sacramento City College, 3835 Freeport Boulevard, Sacramento, CA 95822, US.

References

1. F. Krafft, *Im Schatten der Sensation: Leben und Wirken von Fritz Straßmann*. Weinheim: Verlag Chemie, 1981.
2. R. Feyl in *Der lautlose Aufbruch-Frauen in der Wissenschaft*, p 162. Darmstadt: Luchterhand, 1983.
3. O. R. Frisch, *Biog. Mem. Fell. Roy. Soc.*, 1970, **16**, 405; R. Spence, *Biog. Mem. Fell. Roy. Soc.*, 1970, **16**, 279; R. L. Sime, *J. Chem. Educ.*, 1986, **63**, 653.
4. Otto Hahn, *Erlebnisse und Erkenntnisse*, D. Hahn (ed), p 43. Dusseldorf: Econ, 1975.
5. Letter from Meitner to Max von Laue, 4 September 1944. Meitner collection, Churchill College, Cambridge University.
6. O. R. Frisch, *What little I remember*, p 114. Cambridge: CUP, 1979; O. R. Frisch, *Physics Today*, 1967, **20/11**, 43; R. H. Stuewer, *Perspectives on science* 1994, **2**, 76.
7. O. R. Frisch, *Nature (London)*, 1939, **143**, 276; R. Peierls, *Biog. Mem. Fell. Roy. Soc.*, 1982, **27**, 282.
8. G. Herrmann, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 481; R. L. Sime, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 942.
9. R. L. Sime, *Am. J. Phys.*, 1990, **58**, 262.
10. R. L. Sime, *J. Radioanalytical and Nuclear Chemistry*, 1990, **142**, 3; F. Krafft, *Im Schatten der Sensation: Leben und Wirken von Fritz Straßmann*, chap 3. Weinheim: Verlag Chemie, 1981.
11. Letter from Hahn to Meitner, 19 December 1938. Meitner collection, Churchill College. Cambridge University.
12. O. Hahn and F. Strassmann, *Naturwiss.*, 1939. **27**, 11.
13. L. Meitner and O. R. Frisch, *Nature (London)*. 1939, **143**, 239.
14. N. Bohr, *Phys. Rev.*, 1939, **55**, 418; N. Bohr and J. A. Wheeler, *Phys. Rev.*, 1939, **56**, 426. J. A. Wheeler, *Physics Today*, 1967, **20/11**, 49
15. Letter from Hahn to Meitner, 7 February 1939. Meitner collection, Churchill College Cambridge University.
16. R. L. Sime, *Am. J. Phys.*, (in press, 1994).
17. Letter from Meitner to James Franck, 16 January 1947. Meitner collection, Churchill College, Cambridge University.

ANGEWANDTE
CHEMIE

Volume 30 Number 8
August 1991
Pages 942-953

International Edition in English

Reprint

Lise Meitner and Fission: Fallout from the Discovery

By Ruth Lewin Sime[*]

Much has been written about *Lise Meitner*, but she remains on the periphery. Of her pioneering work in nuclear physics, little is said; she is remembered primarily for nuclear fission, a discovery in which she did not share. Especially in Germany the staging seldom varies: *Otto Hahn* in the spotlight, *Fritz Straßmann* in his shadow, *Lise Meitner* in the wings, dimly outlined in reflected light. Her role is open to speculation. One writer sees her work "crowned by the Nobel Prize for Otto Hahn";[1] another, once director of an institute that bears her name, portrays her as the physicist who obstructed the discovery from the start.[2] Often she is cast as *Hahn*'s *Mitarbeiterin*;[3] sometimes she is completely invisible, as in one of the world's great science museums, which for 30 years displayed[4] the fission apparatus–equipment assembled by *Lise Meitner* on a table in *her* laboratory in *her* physics section of the Kaiser-Wilhelm-Institut für Chemie—without ever mentioning her name.[**] The principals themselves do not agree. In his memoirs, *Hahn* has remarkably little to say of his closest colleague and friend. Only over a glass of wine, we are told, "konnte ihm die Äusserung entschlüpfen: 'Ich weiss nicht; ich fürchte, Lischen hätte mir die Uranspaltung verboten.'"[5] ("he might let slip: 'I don't know; I'm afraid Lischen would have forbidden me to discover fission.'") *Straßmann* insists: "Lise Meitner war die geistig Führende in unserem Team gewesen"![6] ("Lise Meitner was the intellectual leader of our team"!) From *Lise Meitner* herself we have no autobiography. Available, however, is the large collection of letters and documents she has left behind, and these make it possible for us to learn much more.

1. Introduction

The historian *Fritz Stern* has written of this century's most famous scientist, "Einstein and Germany: they illuminate each other."[7] The same can be said of *Lise Meitner*, only more so—because she was more attached to Germany, because she stayed longer and never cut her ties to it, because her best years of work and the bitter consequences of her exile could not be separated from the science, culture, and politics of her German experience.

She came to Berlin from her native Vienna in 1907. Women were still excluded from Prussian universities, yet she found a place of work and a chance to prove herself. Before long Germany was her professional home, the sanctuary that rescued her, as she believed, from a wasted life in Austria.[8] In time the milestones of her career became markers for the inclusion of women into German science; she flourished in Germany's brilliant physics community and became one the great nuclear physicists of her day.

After 1933 her very success in Germany made her cling to what she had and stay too long, and when she was driven out, finally, exile shattered her career and clouded her scientific reputation. In December 1938, five months after *Meitner* fled Berlin, *Hahn* and *Straßmann* identified barium as a product of the neutron irradiation of uranium. This was, as *Meitner* herself put it, "wirklich ein Meisterstück radioaktiver Chemie"[9] ("truly a masterpiece of radiochemistry"); it was also an intrinsic part and the direct result of a team investigation which *Meitner* brought to Berlin, led for four years, and to which she made crucial contributions until the end. There can be no doubt that had *Meitner* been anything other than a "non-Aryan" in exile, she would have fully shared in the discovery.[10] Instead, she—and physics—were eventually blamed for the failure to make the discovery sooner.

In this article I intend to show that *Lise Meitner*'s exclusion arose not from science but from the racial policies and political aberrations of National Socialist Germany, and to show further that her exclusion was unjustly perpetuated—indeed, deliberately reinforced—long after the Third Reich was over. This article is not a comprehensive review of the fission discovery: it is, instead, an alternative perspective, a focus upon *Lise Meitner* and her work. By documenting her leadership of the uranium investigation in Berlin, I wish to emphasize the importance of physics and its essential interplay with chemistry; by showing that *Meitner* remained a de facto member of the Berlin team until the discovery and beyond, I intend to make clear that political, not scientific, considerations kept her from being acknowledged. Finally, I wish to examine the aftermath of the discovery, during which *Meitner*'s exclusion was codified, physics blamed, and history distorted. For this I shall turn primarily to *Otto Hahn*, who claimed the discovery for chemistry alone, and whose singular prominence in postwar Germany ensured that his version would dominate. Fifty years have passed: there is a need for balance. With this article I seek to reintegrate *Meitner* with the discovery, physics with chemistry, science into its historical and political context

---

[*] Dr. R. L. Sime
Department of Chemistry
Sacramento City College
Sacramento, CA 95822 (USA)

[**] On 4 July 1991 the Deutsches Museum placed a bust of Lise Meitner in the *Ehrensaal*, where busts, reliefs, and portraits of 38 renowned scientists discoverers, and inventers are displayed, including Nikolaus Copernicus, Johannes Gutenberg, Carl Benz, Conrad Röntgen, Max Planck, Albert Einstein, and Otto Hahn

2. The Beginnings of the Uranium Project

Although the discovery of fission is certainly an important chapter in the history of chemistry,[11] it was driven by fundamental questions of nuclear physics. The physicist who originated the investigation was *Enrico Fermi*; the physicist who brought it to Berlin and framed it at every step was *Lise Meitner*. Some years later, in 1944, she described the beginnings to *Max von Laue*. She was in Stockholm by then, unhappy with her working conditions; *von Laue* had suggested that her dissatisfaction was due to the absence of *Otto Hahn*:

> ..so ist Ihre strikte Erklärung, es fehle mir die Zusammenarbeit mit Otto, so irrig, dass ich, verzeihen Sie, lieber Freund, etwas lächeln musste. Otto und ich haben von 1920–1935 auf ganz getrennten Gebieten gearbeitet, er hat sich sogar nach eigenem Gestandnis gar nicht für meine physikalischen Probleme interessiert und wir sind dabei sehr gute Freunde geblieben. Dass wir dann nach so langer Zeit wieder gemeinsam gearbeitet haben, lag daran, dass mich die Fermi'schen Untersuchungen brennend interessiert haben und es mir zugleich klar war, dass man mit Physik allein auf diesem Gebiet nicht weiter kommen konnte. Es musste ein so ausgezeichneter Chemiker wie Otto mithelfen, wenn es Erfolg haben sollte. Ich habe mehrere Wochen gebraucht, bis ich Otto dafür interessiert hatte, er wird es Ihnen gern bestätigen, dass es sich so verhält.[12][*]

2.1. Neutron Irradiations

The investigations which so interested *Lise Meitner* began in Rome in March 1934[13, 14] when Fermi and his co-workers sought to induce nuclear reactions and create new radioactive isotopes by irradiating elements with neutrons. Proceeding systematically through the periodic table, they succeeded first with fluorine and then aluminum;[15] two weeks later they reached lanthanum and reported nearly 20 more.[16, 17] The Italian scientists sent their results to *Ricerca Scientifica*, and mailed preprints a few days later to 40 or so of the most prominent and active nuclear physicists worldwide.[18, 19] *Lise Meitner* was thus among the first to learn of the work in Rome; by May she had verified[20] their neutron irradiations of Al, Si, P, Cu, and Zn, observing the first three in a cloud chamber and measuring the half-lives of the activ ities formed.

2.1.1. *Lise Meitner's Background*[21–26]

Expert in radioactivity and familar with neutron reac tions, *Meitner* was in a perfect position to pursue these ex periments. Her work in radioactivity went back to 1906 i Vienna; from 1907 in Berlin she and *Otto Hahn* identifie several new radioisotopes, developed techniques of radioa tive recoil, pioneered in magnetic beta spectra, and in 191 discovered protactinium ($Z = 91$).[27] By then they were the Kaiser-Wilhelm-Institut für Chemie in Berlin-Dahlem each heading their own section. About 1920, when radioa tivity no longer seemed to promise fundamental new i sights,[28] *Meitner* turned to the infant field of nucle physics, while *Hahn* stayed with the refinement and develo ment of radiochemical techniques.

Always close to theory, *Meitner* explored nearly every a pect of experimental nuclear physics: the sequence of r dioactive decay, the continuous beta spectrum, nuclear sca tering experiments, high-energy gamma radiation. She w quick to use and adapt new instruments, among them t Wilson cloud chamber for nuclear reactions and Geig Müller counters for studies of gamma absorption. After t discovery of the neutron and positron in 1932, she used t cloud chamber to determine neutron mass, and she was first to observe electron–positron pair formation. *Otto Ha* would later remember this as a period when her work, more than his, brought international recognition to th institute.[29] In addition to her own students and assistan *Meitner* frequently welcomed foreign visitors to the institu One of them was *Franco Rasetti*, an associate of *Fermi*, w spent most of the year 1932 in Dahlem learning the nucl techniques—radioactivity, neutron sources, cloud cha ber—needed for the new experimental program in Rome

---

[*] Your assertion that what is missing for me is the collaboration with Otto is so much in error that—forgive me, dear friend—I had to smile a little. Otto and I worked from 1920 to 1935 in completely separate fields; he in fact admitted that he was not at all interested in my physics problems and still we remained good friends. That we worked together once again after such a long time was due to the fact that Fermi's investigations were of consuming interest to me, and it was at once clear to me that one could make no progress in this field with physics alone. The help of an outstanding chemist such as Otto was needed to get results. It took me several weeks to get Otto interested; he will gladly verify for you that it went that way

Ruth Lewin Sime was born in New York City in 1939, graduated from Barnard College in 1 and obtained her doctorate in chemistry from Harvard University under William Lipscom 1964 for X-ray diffraction studies of molecular structures. Since then she has been eng primarily in teaching chemistry, she is involved with programs designed to increase the repre tation of women and minority students in math-based sciences. Her interest in Lise Meitner b some 15 years ago when she taught a women's studies course on "Women in Science" discovered, to her surprise, that little scholarly attention had been paid to Meitner's life and w She is currently completing a scientific and personal biography of Lise Meitner.

had, that the 13-min and 90-min activities might well be elements 93 and 94

Meitner and *Hahn* soon realized that the 13-min and 90-min activities were themselves mixtures[48] and in mid-1935 asked *Straßmann* to join them full-time. Their team was bound by political affinity as well: *Meitner*, "non-Aryan"; *Hahn*, anti-Nazi; *Straßmann*, the exceptionally principled younger man whose aversion to National Socialism and refusal to join the NS-associated *Verein Deutscher Chemiker* isolated him within the institute and made him unemployable outside.[49]

3. "Wege und Irrwege"—Roads and Mistaken Roads

Later, *Lise Meitner* would describe the road to the discovery of fission as "astonishingly long and in part a mistaken road" ("erstaunlich lang und zum Teil ein Irrweg".[9] *Fermi*, *Meitner*, indeed all who worked on the uranium investigation were misled by two false premises, one from physics—that only small changes would occur in nuclear processes—and the other from chemistry—that elements beyond uranium would be higher homologues of the third-row transition elements Re, Os, Ir, Pt, etc. When neutron irradiation of uranium yielded new beta activities which coprecipitated with platinum and rhenium sulfides, the two assumptions unluckily dovetailed—and even after the discovery of fission proved the first one wrong, scientists still did not suspect that the second was wrong as well.[50]

However mistaken, these false premises do not entirely account for the failure to explore alternatives. *Ida Noddack*'s suggestion[51] of a major nuclear breakup was never seriously considered;[52] *Noddack* herself did not pursue it; *Max Delbrück*, *Meitner*'s *Haustheoretiker* for a time, remembered with chagrin how he helped in the "Holzweg der zahllosen 'Transuran'-Isomere" (the "bog of countless 'transurane' isomers") instead of finding a way out.[53]

There was something dazzling about elements beyond uranium.[54] That, coupled with the great difficulty of identifying weak new activities in the presence of the strong natural radioactivity of uranium, led the Berlin team to investigate only the platinum sulfide precipitate, which, they presumed, contained the "transuranes". For the most part they ignored the filtrate, assuming it contained nothing more than uranium and its natural decay products. This was a mistake, *Meitner* remembered:

> Unsere Fällungen bei Bestrahlung mit schnellen Neutronen wurden immer so ausgeführt, daß U, Pa und Th im Filtrat bleiben mußten, wodurch wir meinten eine gewisse Stütze für die Transurannatur der gefällten Elemente zu gewinnen. Darum haben wir – und das war unser Irrtum – zunächst niemals, auch nicht bei den Versuchen mit verlangsamten Neutronen, die Filtrate unserer Fällungen untersucht.[9][*]

The oversight was remarkable, because the Berlin group did discover that an important activity, a 23-min U, was produced only when slowed neutrons were used.[55]

> Also ich glaube wirklich unser Unglück war, dass wir die Filtrate nicht untersuchten. Wir konnten sich nicht untersuchen, weil wir das Uran drin gehabt haben, nicht wahr, da konnten wir nichts sehen. Wir hatten zu schwache Bestrahlungsquellen... [D]ie Chemiker wollten absolut nicht, ich habe sie geplagt, sie sollen es machen wie ich dort war, weil ich so unruhig war. Gerade weil ich zu wenig von Chemie verstehe, war ich natürlich immer unruhig über das was nicht gemacht worden ist, aber dann haben es ja Hahn und Strassmann so wunderbar gemacht, also zu der Zeit hat es wirklich keine Chemiker gegeben, die das hätten machen können.[56][*]

Later *Hahn* and his associates would claim the discovery for chemistry alone, blaming the "Irrwege" solely upon physics and its assumption of small nuclear changes. This was not done in a spirit of scientific objectivity—it ignored the mistakes of chemistry and the guidance of physics. Physics did not predict fission, to be sure, but it detected errors chemistry could not; without physics, chemists would not have begun the investigation; without physics they would have had no reason to sustain it.

3.1. Chemistry: Certainty

The scientific literature of the period[57] makes clear that the investigation was fed by chemical data but interpreted by nuclear physics. The dual roles are particularly evident in parallel reports by *Hahn*, the senior author for chemistry, and by *Meitner* for physics. In 1936 and 1937, the Berlin chemists listed three U activities and two parallel "transurane" sequences including two EkaRe (the presumed element 93), two EkaOs (94), one EkaIr (95), and one EkaPt (96), all beta emitters. Of the uranium activities, just one, 23-min U, was chemically certain; the 10-s and 40-s activities, too short-lived for chemical identification, were attributed to U because genetic sequences obtained from radioactivity data indicated they preceded the two EkaRe. Altogether, the fit between the chemistry expected for transuranium elements and the genetic sequences seemed too good not to be true. In 1936: "[D]ie Zuordnung des 2.2-Min- und des 16-Min-Körpers zum Eka-Rhenium ist frei von Willkür; sowohl die genetischen Beziehungen als auch die chemischen Eigenschaften lassen wohl keinen Zweifel über ihre Zugehörigkeit zum Element 93."[58] ("The assignment of the 2.2-min and 16-min activities of EkaRe is unquestionable; not only the genetic relationships but also the chemical properties really leave no doubt they belong to element 93.") And for EkaOs, EkaIr, and EkaPt, "sind wir nach ihrem allge-

---

[*] During irradiation with fast neutrons our precipitations were always conducted so as to keep U, Pa and Th in the filtrate, from which we drew a certain support for the transurane nature of the precipitated elements. Thus we—and this was our mistake—for a time never examined the filtrate, not even in the experiments with slowed neutrons

[*] I really think our misfortune was that we didn't search the filtrate. We couldn't search it because uranium was in it, we couldn't see anything. Our neutron sources were too weak ... The chemists absolutely didn't want to, I begged them to do it while I was there because I was so disturbed by it Because I understood too little chemistry I was naturally always worried about what wasn't done, but then Hahn and Straßmann did such a wonderful job, surely at the time no other chemists could have done it

meinen chemischen Verhalten sicher bezüglich ihrer Gruppen-Zugehörigkeit" ("we are certain from their general chemical properties to which group they belong").[58] In 1937: "Vor allem steht ihre chemische Verschiedenheit von allen bisher bekannten Elementen ausserhalb jeder Diskussion."[59] ("Above all, their chemical distinction from all previously known elements needs no further discussion.")

3.2. Physics: Doubt

As the chemists grew more confident with each new link in the chain of transuranes, the physical interpretation was buckling under a profusion of data. It was *Meitner*'s task to integrate chemistry, radiochemistry, and her own physical experiments into nuclear reactions that made sense. Her recognition that this could not be done sustained the investigation.

To account for three uranium activities, *Meitner* first proposed[60] three different neutron–uranium reactions, but after an exhaustive series of physical experiments she concluded that all three reaction mechanisms appeared the same. She correctly identified the 23-min U as U-239,[61] formed by a typical resonance capture of fairly slow neutrons by U-238. But the 10-s and 40-s U, which headed the two parallel series of "transuranes", also appeared to be U-239: both series varied identically with neutron energy, were produced by fast neutrons and enhanced by thermal neutrons. Together the results were incomprehensible: the triple isomerism of U-239 was problematic, *inherited* triple isomerism persisting for several generations virtually impossible. In 1937 she concluded: "Dieses Ergebnis ist mit den Kernvorstellungen sehr schwer in Übereinstimmung zu bringen."[55] ("This result is very difficult to reconcile with current ideas of nuclear structure.") And in 1938, after thorium showed similar multiple isomerism: "Dieser Erklärungsversuch stößt auf erhebliche Schwierigkeiten..."[62] ("This attempt at an explanation runs into considerable difficulty...") In addition, *Meitner* was always particularly disturbed by the long chain of beta decays EkaRe, EkaOs, EkaIr, EkaPt, and beyond: capture of just one neutron by U-238 should not have produced instability so great that five or more beta decays were required to relieve it:

> [I]ch war immer unglücklich darüber weil ich nicht verstehen konnte, 'wie kann eigentlich die Kernladung steigen bei derselben Masse?' Das war immer, was ich [C. F. von] Weizsäcker gefragt habe: Wie ist das möglich? Also ich war nie glücklich über unsere Versuche vor der fission.[63][*]

In Paris, meanwhile, *Irène Curie* and *Paul Savitch* had examined the entire uranium mixture without chemical separation and reported a strong new 3.5-h beta emitter with unexplained chemical properties.[64] In Berlin they ascribed it to contamination and named it "Curiosum".[65]

4. Escape from Germany

In 1938 came the *Anschluß* and then whispers: "Die Jüdin gefährdet das Institut".[66] ("The Jewess endangers the Institute.") *Hahn* grew nervous, mindful that Prof. *Kurt Heß*, a "fanatic Nazi" ("fanatischer Nationalsozialist")[67] who worked in the *Gastabteilung* (guest section) upstairs in the Kaiser-Wilhelm-Institut für Chemie, was eager for his position. Her dismissal imminent, *Meitner* learned that technical and academic people would be forbidden to leave Germany; she fled secretly on 13 July 1938. Dutch friends, physicists *Dirk Coster* and *Adriaan Fokker*, got her into Holland; *Niels Bohr* and Swedish friends arranged a place for her in *Manne Siegbahn*'s Nobel Institute for Experimental Physics in Stockholm.[68]

4.1. "Radium" Isomers

Meitner and *Hahn* had worked under the same roof for 31 years; their separation was a shock to them both. Intellectually, however, she was not immediately cut off from Berlin. *Meitner* and *Hahn* wrote to each other[69, 70] constantly; she was still very much a member of the team.

On 23 October *Meitner* was inquiring[71] about the Curie–Savitch 3.5-h substance just as a new report[72] by the Paris scientists reached Berlin. Suspecting that the 3.5-h substance might contain radium, *Straßmann* proposed his own cleaner method of separation.[73] "Vielleicht hat sogar ein Ra-Isotop was dabei zu tun" ("Perhaps a Ra isotope has something to do with it"), *Hahn* wrote *Meitner* on 25 October,[74] and a week later;

> Wir sind jetzt *fast* überzeugt, daß es sich um einige – 2 oder 3 – Radiumisotope handelt, die sich in Ac etc. umwandeln... Es wäre uns natürlich sehr lieb, Du würdest Dir den Fall einmal überlegen, wie eine α-Strahlenumwandlung [U(n, α) → Th → Ra] mit wahrscheinlich auch langsamen Neutronen zu Stande kommen kann, und dabei gleich auch wieder mehrere Isomere...[75][*] (text highlighted in the original is here printed in italics)

Meitner responded instantly:

> Ich will mir brennend gern überlegen, wie Ra od[er] Ac Isotope entstehen können, wenn Du mir nur tatsächlicher schreiben wolltest... Warum glaubt Ihr daß mehrere Körper da sind, habt Ihre mehrere Halbwertszeiten? Warum glaubt Ihr daß es verstärkbar ist? Habt Ihr mit langsamen Neutronen erheblich mehr bekommen? Und wie stark ist denn die Aktivität... verglichen mit dem 16 Min K[örper (Eka-Re)]?... Bitte sei lieb und beantworte alle Fragen. Auch wenn es noch nicht so definitiv ist...[76][**]

---

[*] I was always unhappy about it because I couldn't understand 'How can the nuclear charge increase [so much] with the same mass?' That's what I always asked Weizsäcker: How can that be? You see, I was never satisfied with our experiments before fission.

[*] We are now *almost* convinced that we are dealing with several—2 or 3—radium isotopes which decay to actinium, etc... Naturally, we would like it very much if you could think about the situation, how an α-transformation [U(n,α) → Th → Ra] can come about, probably also with slow neutrons, and at the same time produce several isomers..

[**] I am extremely eager to think over how Ra or Ac isotopes could be produced, if you would only write more factual details Why do you think it is several substances, do you have several half-lives? Why do you think it can be enhanced? Did you get considerably more with slow neutrons? How strong is the activity... compared to the 16-min [EkaRe]? . Please be nice and answer all these questions. Even if it's not yet so definite

The reaction conditions, *Otto Hahn* replied,[77] were essentially the same as for the transuranes. In *Naturwissenschaften* he and *Straßmann* listed three Ra and three Ac isomers and emphasized, "Hier liegt also wohl zum ersten Male der Fall einer *α-Strahlenabspaltung mit verlangsamten Neutronen vor*"[78] ("Here surely for the first time is a case of *α-particles being split off by slow neutrons*.")

4.2. Meeting in Copenhagen

A week later *Lise Meitner* and *Otto Hahn* met in Copenhagen, both invited to *Bohr*'s Institute for Theoretical Physics. There, face-to-face, *Meitner* could make clear to *Hahn* that something was terribly wrong with the new Ra-Ac isomers: an (n, α) reaction induced by slow neutrons was truly impossible.

Their meeting took place three days after the *Kristallnacht*; it was a secret outside Copenhagen. And years later in his memoirs, *Hahn* never mentioned it, although he did recall *Bohr* being "skeptical" and "quite unhappy"[79, 80] ("ziemlich unglücklich") about the radium isomers, and he even remembered talking to *Meitner*'s nephew *Otto Robert Frisch*.[65] But we know from the guest book in *Bohr*'s institute that *Lise Meitner* was there from November 10 to 17,[81] and we know from *Hahn*'s own pocket calendar[82, 83] that she met his train at 6:48 on the morning of November 13, that they had breakfast together and talked for hours, that the next day, after breakfast with *Niels* and *Margrethe Bohr*, *Lise Meitner* and her nephew took *Hahn* to the station and saw him off on the 11:13 train to Berlin. There is also no doubt that *Lise Meitner* forcefully urged *Otto Hahn* to examine the radium isomers more thoroughly than before: this was the message *Hahn* brought back to Berlin. *Straßmann* remembered clearly:

> Jedenfalls hat sie (laut einer Äußerung von O. Hahn) dringend darum gebeten, diese Experimente noch einmal sehr sorgfältig und intensiv zu überprüfen … Zum Glück hatte L. Meitners Ansicht und Urteil bei uns in Berlin ein so großes Gewicht, daß die erforderlichen Kontrollversuche sofort unternommen wurden.[84][*]

4.3. *Barium: "Eine Art Arbeit zu Dreien"*

A few days later *Hahn* and *Straßmann* began the fractional crystallization experiments which led directly to the discovery of barium.[85, 86] From their own statements, we know they still regarded *Meitner* as a member of their team. *Straßmann* wrote later:

> Was bedeutet es, daß Lise Meitner nicht *direkt* teilhatte an der 'Entdeckung'?? Ihrem Impulse ist der Beginn des gemeinsamen Weges mit Hahn, ab 1934, zuzuschreiben – *4 Jahre danach gehörte sie zu unserem Team* –, anschließend war sie von Schweden aus gedanklich mit uns verbunden … Hahn hatte gründliche radiochemische, nur übliche analytische Kenntnisse—bei mir war es umgekehrt, und die Analytik gab den Ausschlag! Aber es ist meine Überzeugung: Lise Meitner war die geistig Führende in unserem Team gewesen, und darum gehörte sie zu uns – auch wenn sie bei der "Entdeckung der Kernspaltung" nicht gegenwärtig war.[6][*]

At the time *Hahn* felt the same. He informed *Meitner* about barium on December 19, without speaking to any of the institute physicists:[87] "Ich habe mit Straßmann verabredet, dass wir vorerst nur Dir dies sagen wollen." ("Strassmann and I have agreed that for now we shall tell only you.") The barium finding was a "schreckliche[r] Schluß" ("frightful conclusion"); he pleaded for interpretation:

> Vielleicht kannst du irgend eine phantastische Erklärung vorschlagen … Falls Du irgendetwas vorschlagen könntest, das Du publizieren könntest, dann wäre es doch noch eine Art Arbeit zu Dreien![88][**]

Anxious to publish quickly, *Hahn* did not wait for *Meitner*'s reply before submitting the article to *Naturwissenschaften* on 22 December. He[89] mentioned the barium results only at the end, after pages of radium data, and then "with hesitation" ("zögernd"). His report expresses the chemistry-physics duality that had characterized the entire investigation. From the chemistry he drew confidence—"Als Chemiker müßten wir … statt Ra, Ac, Th die Symbole Ba, La, Ce einsetzen"[***]—and from physics, doubt: "Als der Physik in gewisser Weise nahestehende 'Kernchemiker' können wir uns zu diesem, allen bisherigen Erfahrungen der Kernphysik widersprechenden, Sprung noch nicht entschließen …"[90][***] To *Lise Meitner* he wrote:[88] "Wir wissen dabei selbst, dass es eigentlich nicht in Ba zerplatzen *kann*! … Also überleg Dir noch, ob sich nicht irgendeine Möglichkeit ausdenken liesse; so etwa Ba-Isotope mit viel höheren A.G. [Atomgewicht] als 137?"[****] *Hahn* had not yet realized that uranium had split in two.[91]

Lise Meitner received *Hahn*'s letter on December 21, her first news of the barium finding. She answered by return mail:

> Mir scheint vorläufig die Annahme eines so weitgehenden Zerplatzens sehr schwierig, aber wir haben in der

---

[*] In any case (according to what O. Hahn said) she urgently requested that these experiments be very carefully and intensively scrutinized one more time … Fortunately, L. Meitner's opinion and judgement carried such weight with us in Berlin that we immediately undertook the necessary control experiments

[*] What did it matter that Lise Meitner did not *directly* participate in the "discovery"?? Her impulse was the beginning of the work with Hahn from 1934, *4 years later she belonged to our team*; in addition she was in close contact with us from Sweden … Hahn was thoroughly versed in radiochemistry, only the usual analytical knowledge—with me it was the reverse, and analytical chemistry achieved the result! But I am convinced, L. Meitner was the intellectual leader of our team, therefore she was one of us, even if she was not actually present for the "discovery of fission"

[**] If there is anything you could propose which you could publish, then after all it would still in a way be work by the three of us!

[***] As chemists we should substitute the symbols Ba, La, Ce for Ra, Ac, Th … As "nuclear chemists" fairly close to physics we can not yet resolve to take this step which goes against all previous experience in nuclear physics

[****] We ourselves know that it cannot really break apart to Ba! … You should reconsider whether there isn't some other possibility; for example, Ba isotopes with much higher atomic weights than 137?

> Kernphysik so viele Überraschungen erlebt, dass man auf nichts ohne weiteres sagen kann: es ist unmöglich[92][*]

Hahn must have been surprised and relieved. In November *Meitner* had vehemently objected to the radium isomers; now she was puzzled but not opposed, intuitively ready to consider the barium result an expansion rather than a contradiction of previous experience in nuclear physics.

Years later, *Hahn* was known to say that had *Lise Meitner* remained in Berlin, she might have talked him out of the discovery, might have "forbidden" him to make it.[93] Clearly, *Meitner*'s letter of 21 December says just the opposite—and at the time *Hahn* must have found it most reassuring, because only after he received it on 23 December did he add to the *Naturwissenschaften* galley proofs a paragraph suggesting that the uranium nucleus has split in two.[94] This strengthened the article, showing that *Hahn* and *Straßmann* had not just identified barium, but understood that fission had taken place. Meanwhile, during their holiday together between Christmas and New Year's Day, *Meitner* and her nephew *Otto Robert Frisch* did propose and prepared to publish the first theoretical interpretation of the fission process.[95]

Meitner's contributions to the discovery thus formed a continuum from the first work in Berlin to the discovery of barium and beyond. At the end only her physical presence was missing. *Meitner* and *Hahn*'s own experience shows that physical presence is not required at all times for every member of a team: in 1917 and 1918 when *Hahn* was in the army, *Meitner* did nearly all the work, and both, without question, were credited with the discovery of protactinium.[27, 96] In 1938 *Lise Meitner* was excluded only because the same racial policies that had driven her from Germany made it impossible for her to be part of the barium publication, made it uncomfortable, as we shall see, for *Hahn* to even admit his ongoing collaboration with a "non-Aryan" in exile.

4.4. Transmutation: "Wir haben die Physik absolut nicht berührt..."

Meitner knew nothing could be done;[97] congratulating *Hahn* and *Straßmann* for their "beautiful finding" ("wunderschönes Ergebnis") she could not help but add; "I stand here with very empty hands." ("wenn ich jetzt auch mit sehr leeren Händen dastehe."[98]) It was worse, for while her name was missing from the discovery of barium, it was still firmly associated with the false "transuranes", which *Meitner* now understood to be fission fragments, not elements beyond uranium at all.

The timing was bad: *Meitner* was struggling to make a new start in Stockholm. She feared for her reputation, worried that people might say: "[D]ie Drei haben also Unsinn gemacht, und jetzt nach dem Weggang des einen haben die zwei andern das in Ordnung gebracht."[99] ("The three must have done nonsense, and now that one is gone the other two made it right.") She hoped[100] *Hahn* would say in his next paper that the discovery of barium was based upon techniques and results they had developed together. She could not imagine that *Hahn* himself would soon suppress and deny not only her ongoing collaboration, but the value of nearly everything she had done before.

On 16 January 1939 *Meitner* and *Frisch* sent their theoretical explanation of the fission process to *Nature*.[101] They described the nucleus as a classical liquid drop, its surface tension diminishing under increasing charge, dividing in two, converting mass into 200-MeV energy, forming neutron-heavy fission fragments whose long chain of beta decays finally made sense. It was a good piece of work, *Meitner* knew. Although it could not compensate for being excluded from the discovery itself, it tied her to it, permitted her to be the first to lay inherited isomerism and the "transuranes" to rest, and allowed her to salvage one earlier result: the 23-minute U-239 was still valid and the precursor of the first true element 93.

Meanwhile in Berlin the barium report appeared in *Naturwissenschaften* on 6 January 1939—and physicists in the institute were most upset that they had not been told before. *Hahn* was vulnerable, surrounded by Party members of all degrees of enthusiasm and opportunism, worried about the ambitious and dangerous Prof. *Heß* in the *Gastabteilung* upstairs.[102] When he wrote the next Hahn–Straßmann paper[103] at the end of January, *Hahn* gave only the briefest mention to *Meitner*'s earlier contributions and barely acknowledged the theoretical interpretation of *Meitner* and *Frisch*.[104]

Meitner reacted with despair. To her brother she wrote:

> Hahn hat jetzt in Fortsetzung unserer letzten gemeinsamen Arbeiten ganz wunderbare Dinge gefunden... Und so sehr mich diese Resultate wissenschaftlich und persönlich für Hahn freuen – so denken hier jetzt manche Menschen, dass ich überhaupt nichts gemacht habe.[105][*]

In Stockholm, she wrote to *Hahn*, she had a room in *Siegbahn*'s institute but no equipment, no help, no rights; she had ideas for experiments but could not do them, and she did not get along with *Manne Siegbahn*:

> Jetzt wird Siegbahn allmählich glauben – besonders nach Euern so schönen Ergebnissen, dass ich überhaupt nichts gemacht habe und Du auch die ganze Physik in Dahlem gemacht hast. Ich verliere allmählich allen Mut. Verzeih diesen unfrohen Brief. Ich weiss manchmal nicht mehr, was ich mit meinen Leben anfangen soll. Wahrscheinlich geht es vielen, die weggegangen sind, so wie mir, aber darum ist es doch sehr schwer.[106][**]

---

[*] To me at the moment the assumption of such a large-scale breakup appears very difficult, but we have experienced so many surprises in nuclear physics that one can not unconditionally say: it is impossible

[*] Hahn has just published absolutely wonderful things based on our work together... And much as this makes me happy for Hahn, personally and scientifically, many people here must think I contributed nothing to it

[**] Now Siegbahn will gradually believe, especially after your beautiful results, that I never did anything and you also did all the physics in Dahlem I am gradually losing all my courage. Forgive this unhappy letter. Sometimes I don't know what to do with my life. Most probably there are many who emigrated who feel as I do, but still it is very hard

Hahn responded with a list of physicists and their complaints:

> Ich fürchte, es wird mir auch etwas übel genommen, daß wir strikte nichts über unsere Versuche erzählten... [Ich] möchte den Herren [Physikern im Institut] aber doch nicht beichten, daß Du der Einzige warst, der sofort alles erfahren hat... Wie Du glauben kannst, Siegbahn denkt, Straßmann und ich machten auch die Physik, verstehe ich nicht. Wir haben bei der ganzen Arbeiterei die Physik absolut nicht berührt, sondern immer und immer wieder nur chemische Trennungen gemacht. Wir kennen doch unsere Grenzen und wissen natürlich auch, daß in diesem besonderen Falle es zweckmäßig war, nur Chemie zu machen... [D]ie Arbeit über das Uran [ist mir] ein vom Himmel gesandtes Geschenk. Ich fürchte nämlich manchmal, daß Dr. K.[107] dem Herrn... allmählich Teile des Instituts geben will...[108][*]

In this letter *Hahn* reveals the fear that drove him, in just two months, to transmute "eine Art Arbeit zu Dreien" into a work that "absolutely did not touch upon physics". By redefining the discovery to be just those chemical separations he and *Straßmann* had done in December, he divorced fission from physics—and himself from *Lise Meitner*.

5. Priorities

Hahn never retreated from this view. Throughout the spring of 1939 he was in a state of constant anxiety, fearful of losing priority for his "heaven-sent gift". As physicists worldwide rushed into print, they occasionally failed to cite *Hahn* and *Straßmann* fully. *Hahn* was defensive and irritable: he quarrelled with *Meitner*, with *Bohr*, with English colleagues; when *Lise Meitner* suggested he might have been more generous to *Curie* and *Savitch* he was annoyed;[109] when *Ida Noddack* chastised him for failing to mention her 1934 paper, he refused to answer.[110] As a non-Nazi he was feeling isolated in Germany; as a German, estranged from scientists abroad. Even as a chemist he felt left out. Having convinced himself the discovery owed nothing to physics, he was irritated to see the development of fission so throughly dominated by physicists, the more so because he had trouble understanding what they were doing. He never developed a close relationship with physicists in his institute; it was *Lise Meitner* who patiently explained things to him.[111] Finally, by the summer of 1939, his institute seemed secure, his position safe: "Die 'Uranspaltung' hat da die ganze Situation gerettet."[66] ("Fission saved the entire situation.")

6. The Bomb

During the war *Lise Meitner* and *Otto Hahn* corresponded cautiously, avoiding politics, the war, fission. In Sweden *Meitner* felt forever homeless,[112] unwelcome in *Siegbahn*'s institute, isolated from nuclear physics. To her distress she saw herself become a nonperson in Germany, her work either ignored entirely[113] or cited using an "Auswahlprinzip bei Zitieren"[114] ("selection principle for citation")—that is, with her name omitted. She tried not to dwell on her troubles; much as she wished for the defeat of Germany, she agonized over the war casualties on both sides.[115] In 1943 she was asked to join the British scientists bound for Los Alamos. It would have meant escape from Sweden, interesting physics, valued colleagues. But she could not do it: "I will not work on a bomb!"[116] She knew very little of the corresponding German effort, only that it existed, that *Werner Heisenberg* was in charge and *Hahn* involved—enough to be anxious whenever reports came in of powerful new German weapons.[117]

When the war in Europe ended without an atomic bomb, she was greatly relieved; the news of Hiroshima came as an enormous shock.[118] For weeks the press swarmed around her, made up interviews when she refused to talk to them, got the facts wrong when she did.

Otto Hahn meanwhile was interned in Farm Hall, a country estate near Cambridge, England. He, too, was shocked by the bomb, then upset that the scientist of the day was not he, but *Lise Meitner*. In his memoirs, he noted: "Zum Teil unwahre Angaben über die Entdeckung; besonders am Anfang spielt Lise Meitner dabei eine große Rolle, ich selbst werde nicht genannt."[119] ("Partly untrue articles about the discovery; especially in the beginning Lise Meitner played a large role. I myself was not mentioned.") On 8 August 1945, two days after President *Truman*'s announcement of the first bomb, *Hahn* prepared a press release:

> So lange Prof. Meitner in Deutschland war, war von einer Spaltung des Urans keinerlei Rede. Sie wurde für unmöglich gehalten. Auf Grund von ausführlichen, chem. Untersuchungen über die bei der Bestrahlung des Urans mit Neutronen auftretenden chemischen Elemente wurden Ende des Jahres 1938 Hahn und Strassmann zu der Annahme gezwungen, dass bei diesen Vorgängen das Uran in zwei Teile zerplatzt, von denen ein Teil, das chem. Element Barium, sicher nachgewiesen wurde... Mit ihrem Neffen, Dr. O. R. Frisch gab [Prof. Meitner] eine Erklärung für diese von Hahn und Strassmann experimentell gefundene, bisher für unmöglich gehaltene "Atomspaltung".[120][*]

This was the summer of 1945; it could have been a new beginning, a time to set the record straight, to recall *Meitner*'s part in the Berlin team and the discovery of fission.

---

[*] I fear it is held against me that we said nothing to anyone about our findings... I do not want to confess to these gentlemen that you were the only one who learned of everything immediately... I don't understand how you can believe that Siegbahn thinks Straßmann and I also did physics. In all our work we absolutely did not touch upon physics, but instead we did chemical separations over and over again. We know our limits and also know of course that in this case it was useful to do only chemistry... [For me] the uranium work [fission] is a heaven-sent gift. Namely, I was fearful sometimes that... Dr. K. wants gradually to turn over parts of the institute to Herr

---

[*] ...As long as Prof Meitner was in Germany, there was no discussion of the fission of uranium. It was considered impossible Based on extensive chemical investigations of the chemical elements resulting from neutron irradiation, Hahn and Strassmann were forced to assume at the end of 1938 that uranium splits into two parts... of which one part, the element barium, was identified with certainty... With her nephew, Dr O R. Frisch, [Prof Meitner] explained these experimental findings of Hahn and Strassmann, the 'atom-splitting' which until then had been considered impossible

Instead, *Hahn* was taking care to create the impression that *Meitner* had done nothing for fission except "consider it impossible" and prevent it from being discoverd earlier

7. Suppressing the Past

Hahn was calling upon fission to serve again—not himself this time, but his defeated country. He had already been awarded the 1944 Chemistry Nobel Prize—in secret, but he knew. He would use his personal prestige and the importance of the discovery to call attention to Germany's misery, to rebuild German science. To do this, he felt it necessary to make the discovery his, and his alone. He saw no purpose in looking back to the injustices of the Nazi period; he felt no personal necessity to make amends. With the Third Reich gone, the old nationalism resurged. *Hahn* was concerned for Germany—and only Germany.

Meitner had sensed this attitude even before the end of the war. In March 1945 she wrote to a Swedish friend:

> Die Briefe der deutschen Freunde klingen sehr gedrückt und doch glaube ich nicht, dass sie ganz erfasst haben, welchem Schicksal sie Deutschland durch ihre Passivität ausgeliefert haben. Und noch weniger scheinen sie sich bewusst, dass sie ein Stück Mitverantwortung haben für die schrecklichen Verbrechen, die Deutschland begangen hat. Dieser Gedanke macht mich richtig unglücklich. Wie soll die Welt Vertrauen zu einem neuen Deutschland haben, wenn seine besten und geistig höchst stehenden Vertreter nicht diese Einsicht haben und nicht den brennenden Wunsch haben, gut zu machen, was gut zu machen ist. Sie müssten das nicht nur stark fühlen, sondern sich zur gegebenen Zeit offen dazu bekennen. Aber ich fürchte, davon sind sie noch sehr weit entfernt. Darum glaube ich auch nicht an einen Widerstand "en masse" von innen heraus.[121][*]

Otto Hahn was released from Farm Hall in January 1946 and returned to a Germany that was hungry, cold, utterly destitute. His letters to *Lise Meitner* were a litany of hardships. *Meitner* sympathized, she sent packages—more than she could afford—but she could not stand *Hahn*'s nationalistic self-absorption. When *Otto Hahn* complained about food shortages, demeaning travel restrictions, and requisitioned apartments, *Lise Meitner* responded sharply that Germany had inflicted suffering and death upon millions;[122] when he wrote," [O]b das Verhalten der Besatzungsmächte heute so sehr großzügiger ist als das der Deutschen in Teilen der besetzten Länder, möchte ich fast bezweifeln"[123] ("I almost doubt that the behavior of the current occupation forces is so much nobler than that of the Germans in the occupied countries"), *Meitner* was aghast and reminded him of the millions murdered by Germans in occupied Poland.[124] They fought continuously until December 1946, when *Otto Hahn* and his wife *Edith* came to Stockholm for his Nobel Prize. *Meitner* expected their visit to be an "Eiertanz"[125]—like walking on eggs—but she was determined to be friendly

Hahn came to Stockholm not only to claim his Prize, but to plead for Germany.[126] *Lise Meitner* was prepared for that, but she did not fully realize until then that she no longer had a place in *Hahn*'s life, or even his memory. In his many press interviews, he never spoke of their work together; not once did he even mention her name. In his Nobel lecture[37] he could not omit her entirely, but he gave no sense of their teamwork and emphasized instead that the discovery had been made in opposition to the experience of nuclear physics.

After the *Hahn*s left, *Lise Meitner* tried to sort things out in letters to friends:

> Dass [Hahn] mit keinen Wort mich in seinen Inverviews erwähnt hat, geschweige von unserer mehr als 30jährigen Zusammenarbeit etwas gesagt hat, fand ich etwas schmerzhaft. Was ihn dazu veranlasst haben mag, ist komplizierter Natur. Er ist überzeugt, dass den Deutschen Unrecht geschieht und das umso mehr als er die Vergangenheit einfach verdrängt. Daher war sein einziger Gedanke hier für Deutschland zu sprechen. Ich bin ein Teil der zu verdrängenden Vergangenheit und das umso mehr als ich bevor er hierher kam... versuchte, ihn darauf aufmerksam zu machen, dass die anständigen Deutschen Deutschland nur helfen können, wenn sie die Geschehnisse objectiv sehen...[127][*]
>
> In seinem... Interview, sagte er... er sei glücklich, dass sich Deutschland nicht mit der Schuld der Konstruktion einer Atombombe und dem sinnlosen Töten von so vielen tausend Menschen belastet hätte. Ich versuchte ihm klar zu machen, dass er das wohl hätte sagen dürfen, wenn er dazu gefügt hätte, er sei darum darüber froh, weil die Deutschen ja so viel Schreckliches getan hätten. Aber darauf ging er wieder nicht ein... [E]r verdrängt die Vergangenheit mit aller Macht, obwohl er die Nazi wirklich immer gehasst und verachtet hat. Aber da sein zweites Hauptmotiv ist, Deutschland wieder zu internationalem Ansehen zu bringen und er weder ein starker Charakter, noch ein sehr nachdenklicher Mensch ist, leugnet er einfach das Geschehene oder bagatellisiert es...[128][**]

---

[*] The letters from German friends sound very depressed, yet I don't think they comprehend just what fate has befallen Germany through their passivity And they understand even less that they bear some responsibility for the horrible crimes Germany has committed. These thoughts make me terribly unhappy. How shall the world trust a new Germany when its best and intellectually most prominent people do not have the insight to understand this and do not have a burning desire to make whatever amends are possible? They must not only feel this strongly, but at the proper time state it openly But I fear they are still far from it. For this reason I do not believe that for the most part they had a strong inner resistance.

[*] I found it quite painful in his interviews Otto didn't say one word about me, let alone our 30 years of work together His motivation is somewhat complicated. He is convinced that Germans are being treated unjustly, the more so in that he simply suppresses the past. Therefore his only thought here was to speak for Germany. I am part of that suppressed past, the more so since before he came... I tried to tell him that decent Germans can help Germany only by seeing things objectively.

[**] In one interview he said... he was glad that Germany was not burdened with the guilt of constructing an atomic bomb and causing the needless deaths of so many thousands. I tried to tell him that he certainly might say that, but only if he also said that Germany had done so many terrible things. But he did not respond to that... He suppresses the past with all his might, even though he always truly hated and despised the Nazis. One of his motives is to gain international respect for Germany once again, and since he does not have a very strong character, nor is he a very thoughtful person, he deceives himself about the facts, or belittles their importance

In 1947 *Fritz Straßmann* asked *Lise Meitner* to come to Mainz as head of physics and director of the newly relocated Kaiser-Wilhelm-Institut (soon-to-be Max-Planck-Institut) für Chemie.[129] She considered the offer, but only because she valued *Straßmann*; then she refused.[130] To a Swedish friend she wrote:

> [D]ie Deutschen [haben] noch immer nicht begriffen, was geschehen ist und alle Greuel, die nicht ihnen persönlich widerfahren sind, völlig vergessen. Ich glaube, ich würde in dieser Atmosphäre nicht atmen können.[131][*]

Ten years after fleeing Germany, *Meitner* finally understood she could not return.

8. Postscript: "die *Mitarbeiterin*"[3]

Meitner did not continue her battles with *Hahn*. A nostalgic warmth gradually returned to their friendship, and she often visited Germany for lectures and conferences. Underneath, nothing was resolved. *Hahn* became postwar Germany's major scientific hero: Nobel laureate, president of the Max-Planck-Gesellschaft, prototype of the "decent German", lionized at every turn. *Meitner*, in every sense the outsider, was witnessing the disappearance of her scientific past. In 1953 she wrote to *Hahn*:

> Jetzt möchte ich etwas Persönliches schreiben, das mich bedrückt und das ich Dich bitte in Erinnerung an unsere mehr als 40-jährige Freundschaft und mit dem Wunsch, mich zu verstehen, zu lesen. In dem Bericht der Max-Planck-Gesellschaft wird der Vortrag, den ich in Berlin gehalten habe (ein rein physikalischer Vortrag) angeführt und ich werde genannt als "langjährige Mitarbeiterin unseres Präsidenten." Gleichzeitig habe ich in der Naturwissenschaftlichen Rundschau einen Artikel von Heisenberg gelesen über die Beziehungen zwischen Physik und Chemie in den letzten 75 Jahren, wo die einzige Erwähnung von mir... lautet: "Die langjährige Mitarbeiterin Hahns, Frl. Meitner."[132] Ich bin im Jahr 1917 vom Verwaltungsrat des K.W. für Chemie offiziell mit der Einrichtung der Physikalischen Abteilung betraut worden und habe sie 21 Jahre geleitet. Versuche Dich einmal in meine Lage hineinzudenken! Was würdest Du dazu sagen, wenn Du nur charakterisiert würdest als der langjährige Mitarbeiter von mir? Soll mir nach den letzten 15 Jahren, die ich keinem guten Freund durchlebt zu haben wünsche, auch noch meine wissenschaftliche Vergangenheit genommen werden? Ist das fair? Und warum geschiehtes?[133][**]

It is unlikely that *Hahn* understood; certainly he never spoke out on *Meitner*'s behalf. On the contrary, in his autobiographies[40, 41] his treatment of *Lise Meitner* the person was utterly perfunctory—except for a few coarse anecdotes[134] she appears more a ghost than a real human being. His protrayal of *Lise Meitner* the scientist gives little sense of their early collaboration or her independent work, no mention of her initiative in 1934, her leadership of the Berlin team, their crucial meeting in Copenhagen, her encouragement later. Apparently written without consulting scientific literature, correspondence, or his own personal diaries, *Hahn*'s autobiographies reveal a memory so faulty, superficial, selective, and self-serving that his character and motives must be called into question. It may be that *Hahn*'s self-deception and absence of feeling, which served as a survival tactic under a terror regime, congealed so irreversibly in the post-war period that it became impossible for him to examine the past. *Lise Meitner*, in her Viennese way, simply said: "Man kann wahrscheinlich nicht ein so charmanter Mensch sein und daneben sehr tief sein."[135] ("Probably one can not be such a charming person and also very deep.")

Meitner's public reaction was muted; she had no desire to battle the phenomenon of *Otto Hahn*.[136] Indeed, *Hahn*'s unparallelled celebrity status spawned an enormous quantitiy of derivative biographical material. A chorus of former associates, none close, echoed his contention that fission had nothing to do with physics or *Meitner*. Fission, they insisted, was discovered by the chemists in spite of the physicist.[137] In Germany only *Fritz Straßmann* and *Max von Laue* cared to recognize the obvious: if *Lise Meitner* had not been forced to emigrate, "sie wäre sonst zweifellos in der einen oder anderen Form an der Entdeckung der Uranspaltung mitbeteiligt..."[6, 138] ("she would undoubtedly, in one form or other, have participated in the discovery of fission.")

Had *Lise Meitner* been in Germany in December 1938, the discovery would have been hailed as the brilliant work of an interdisciplinary team. Instead, the politics of race demanded her exclusion. Rather than recognizing this as an injustice, *Hahn* and his followers invented spurious scientific explanations for it: they blamed the victim. Arrogantly, with misplaced national pride, they denied the injustice, created new injustice, perpetuated it—and implicated themselves.

9. Future

Primo Levi has written, "[T]he entire history of the [Third] Reich can be re-read as a war against memory, an Orwellian falsification of memory, falsification of reality, negation of reality."[139] *Lise Meitner*'s experience shows how memory and reality came to be falsified, even by those who were nominally anti-Nazi, even by scientists who were trained to pursue the truth. But for *Meitner*, at least, it appears that a

---

[*] The Germans have still not grasped what has happened and have completely forgotten all atrocities that did not personally happen to them. I think I could not breathe in such an atmosphere.

[**] Now I want to write something personal, which bothers me, and which I ask you to read with our more than 40-year friendship in mind and with the desire to understand me. In the report of the Max-Planck-Gesellschaft there is reference to a lecture I gave in Berlin (a purely physics lecture), and I am named as the long-time *Mitarbeiterin* of our President. At the same time I read an article by Heisenberg in Naturwissenschaftliche Rundschau about the relationship between physics and chemistry in the last 75 years, where the only mention of me... is: "Hahn's long-time *Mitarbeiterin*, Frl Meitner." In 1917 I was given official responsibility by the board of the K W für Chemie to set up the Physics Section, and I led it for 21 years. Try to put yourself in my place. What would you say, if you were only characterized as the "long-time *Mitarbeiter*" of mine? After the last 15 years, which I wouldn't wish on any friend, shall my scientific past also be taken from me? Is that fair? And why is it happening?

genuine rehabilitation is underway: a new generation has begun to illuminate *Lise Meitner*'s scientific past, her life, and the world in which she lived.[140]

I am grateful to Irmgard Straßmann and the late Professor Fritz Straßmann for valuable discussions, to Ulla Frisch and the late Professor Otto Frisch for access to the Meitner Collection in Churchill College, to the late Marie-Luise Rehder for untold help, and to Dr. Marion Kazemi and the Archiv zur Geschichte der Max-Planck-Gesellschaft for access to the archives. I wish to thank Joan Bromberg, Stanley Goldberg, and Pieter Van Assche for critically reading this article. Support by the (U.S.) National Science Foundation and the National Endowment for the Humanities is gratefully acknowledged.

Received: April 5, 1990 [A 829 IE]
German version: *Angew. Chem. 103* (1991) 956

---

[1] R. Feyl: "Lise Meitner 1878–1968" in *Der lautlose Aufbruch – Frauen in der Wissenschaft*, Luchterhand, Darmstadt 1983, p. 162

[2] K.-E. Zimen, *Atomwirtsch. Atomtech. 33* (1988) 588, *Zimen* was director of the Hahn-Meitner-Institut in Berlin.

[3] *Mitarbeiterin* translates as "co-worker", but the German has more connotation of subordinate. For a recent example: H. Rechenberg, *Phys. Bl 44* (1988) 453; also see [4].

[4] The Deutsches Museum's display of the so-called "Arbeitstisch von *Otto Hahn*" mentioned *Straßmann* only at the side and *Meitner* not at all until early 1989, when a small sign was added denoting *Meitner* as *Hahn*'s *Mitarbeiterin*. Recently, the display has been altered to include *Hahn*, *Meitner*, and *Straßmann*, with appropriate changes in the audiotape and written material

[5] W. Heisenberg, *Orden pour le mérite für Wissenschaft und Künste. Reden und Gedenkworte 9* (1968/1969) 111.

[6] F. Straßmann: *Kernspaltung – Berlin Dezember 1938*, Privatdruck, Mainz 1978, p. 23; reprinted in [22], p. 211.

[7] F. Stern: *Dreams and Delusions: National Socialism in the Drama of the German Past*, Vintage, New York 1989, p. 27.

[8] Letter from *Lise Meitner* to *Elisabeth Schiemann*, 31 December 1913, unless otherwise specified, all correspondence is from the Meitner Collection, Churchill College, Cambridge (England).

[9] L. Meitner, *Naturwiss. Rundsch. 16* (1963) 167.

[10] *Max von Laue* expressed this in 1957; see Section 8 and [6, 22]

[11] a) G. Herrmann, *Angew. Chem. 102* (1990) 469; *Angew. Chem. Int Ed Engl. 29* (1990) 481; b) G. Herrmann, *Nucl. Phys. A 502* (1989) 141 c

[12] *Meitner* to *Max von Laue*, 4 September 1944

[13] E. Segrè: *Enrico Fermi: Physicist*, University of Chicago Press, Chicago 1970, p. 73.

[14] E. Segrè (Ed.): *Enrico Fermi: Collected Papers (Note e Memorie)*, University of Chicago Press, Chicago (Accademia Nazionale dei Lincei Roma) 1962, Vol. 1, p. 640.

[15] E. Fermi, *Ric. Sci. 5(1)* (1934) 283; 25 March 1934; Engl. transl in [14] pp. 674–675.

[16] E. Fermi, *Ric. Sci. 5(1)* (1934) 330; Engl. transl. in [14], p. 676

[17] E. Fermi, *Nature (London) 133* (1934) 757; submitted on 10 April 1934

[18] Ref. [13], p. 74

[19] *Meitner* to *Enrico Fermi*, 16 May 1934

[20] L. Meitner, *Naturwissenschaften 22* (1934) 420.

[21] O. R. Frisch, *Biogr. Mem. Fellows R. Soc. 16* (1970) 405.

[22] F. Krafft: *Im Schatten der Sensation. Leben und Wirken von Fritz Straßmann*, Verlag Chemie, Weinheim 1981, Chap. 2

[23] F. Krafft, *Angew. Chem. 90* (1978) 876; *Angew. Chem. Int. Ed Engl 17* (1978) 826.

[24] C. Kerner: *Lise, Atomphysikerin*, Beltz, Weinheim 1986

[25] S. A. Watkins, *Am. J. Phys. 51* (1983) 551

[26] R. L. Sime, *J. Radioanal. Nucl. Chem. 142* (1990) 13

[27] R. L. Sime, *J. Chem. Educ. 63* (1986) 653

[28] L. Badash: *Radioactivity in America*, Johns Hopkins University Press, Baltimore 1979, p. 213. *Badash* speaks of radiochemistry's "suicidal success. . the field effectively ceased to exist"

[29] D. Hahn (Ed.): *Otto Hahn, Erlebnisse und Erkenntnisse*, Econ Verlag, Düsseldorf 1975, p. 43

[30] Ref. [14], p. 548

[31] E. Fermi, E. Amaldi, O. D'Agostino, F. Rasetti, E. Segre, *Ric. Sci. 5(1)* (1934) 452; Engl. transl. in [14], p. 677

[32] E. Fermi, F. Rasetti, O. D'Agostino, *Ric. Sci. 5(1)* (1934) 536; submitted on 6 June 1934

[33] E. Fermi, *Nature (London) 133* (1934) 898; appeared on 16 June 1934

[34] The *Nature* reference is undoubtedly [33], published on 16 June 1934. *Meitner* may have meant *Ricerca Scientifica*, (Refs. [31] or [32]) rather than the *Nuovo Cimento* review articles (E. Fermi, *Nuovo Cimento 11* (1934) 429 and E. Amaldi, E. Fermi, F. Rasetti, E. Segrè, *ibid. 11* (1934) 442) published in July, which included no results not previously reported in *Ricerca Scientifica* and *Nature*. In any event, it is evident that *Meitner* knew of *Fermi*'s uranium results by June

[35] See [29], pp. 40–41, O. Hahn, L. Meitner, *Naturwissenschaften 19* (1931) 738; A. von Grosse, O. Hahn, L. Meitner, *ibid 20* (1932) 362

[36] Ref [29], p. 47.

[37] *Nobel Lectures Chemistry* 1942–1962, Elsevier, Amsterdam 1964, p. 172; also see in [41], p. 253

[38] O. Hahn *New Atoms*, Elsevier, New York 1950, p. 17

[39] O Hahn, *Naturwissenschaften 46* (1959) 158

[40] a) O. Hahn: *Vom Radiothor zur Uranspaltung. Eine wissenschaftliche Selbstbiographie*, Vieweg, Braunschweig 1962, p. 116; b) O. Hahn: *A Scientific Autobiography* (transl. by W. Ley), MacGibbon & Kee, London 1967, p. 141

[41] a) O Hahn: *Mein Leben*, Bruckmann, München 1968, p. 148; b) O. Hahn: *My Life* (transl. by E. Kaiser and E. Wilkins), Herder and Herder, New York 1970, pp. 147–148

[42] A. von Grosse, M. Agruss, *Phys. Rev. 46* (1934) 241

[43] In [41 a] (p. 148) and [41 b] (p. 147) *Hahn* even "remembers" that he and *Meitner* did not learn of *Fermi*'s experiments until they returned from a conference in the Soviet Union in *September* 1934 and were prodded by *Max Delbrück* to repeat them

[44] O Hahn, L. Meitner, *Naturwissenschaften 23* (1935) 37

[45] L. Meitner, *Naturwissenschaften 22* (1934) 759

[46] L. Meitner, *Naturwissenschaften 22* (1934) 733

[47] E. Fermi, E. Amaldi, B. Pontecorvo, F. Rasetti, E. Segrè, *Ric. Sci. 5(2)* (1934) 282–283; Engl. transl. in [14], p. 761

[48] O Hahn, L. Meitner, *Naturwissenschaften 23* (1935) 230.

[49] Ref. [22], pp. 40–47; in 1986 *Straßmann* was posthumously honored by the Israeli Holocaust Memorial (Yad Vashem) for hiding a Jewish friend during the war

[50] E Segrè, *Phys. Rev. 55* (1939) 1104; also [64].

[51] I Noddack, *Z. Angew. Chem. 47* (1934) 653

[52] *E. Amaldi*, a member of *Fermi*'s group, remembers a bias against *Noddack* (Ref. [22], p. 316); this was also true in Berlin. For further discussion, see P. Van Assche, *Nucl. Phys. A 480* (1988) 205.

[53] Ref [22], pp. 103–104

[54] P R. Weart in W. R. Shea (Ed.): *Otto Hahn and the Rise of Nuclear Physics*, Reidel, Dordrecht 1983, p. 105. In Berlin it was hoped that the international attention for the "transuranes" might somehow protect the three political undesirables and their institute.

[55] L. Meitner, O. Hahn, F. Straßmann, *Z. Phys. 106* (1937) 249

[56] L Meitner, interview on 12 May 1963, American Institute of Physics (New York) Oral History Project.

[57] Contemporary reviews include L. Quill, *Chem. Rev. 23* (1938) 87; L. A Turner, *Rev. Mod. Phys. 12* (1940) 1; see also [11 a].

[58] O Hahn, L. Meitner, F. Straßmann, *Ber. Dtsch. Chem. Ges. 69* (1936) 905

[59] O Hahn, L. Meitner, F. Straßmann, *Ber. Dtsch. Chem. Ges. 70* (1937) 1374

[60] L Meitner, O. Hahn, *Naturwissenschaften 24* (1936) 158.

[61] 23-m U-239 necessarily decays to element 93, but the Berlin team, hampered by weak neutron sources and distracted by the other "transuranes", did not detect it; see [11 a].

[62] L Meitner, F. Straßmann, O. Hahn, *Z. Phys. 109* (1938) 538.

[63] Ref [56]; also in [101], *Meitner* wrote: "The long chain of beta decays has always puzzled us."

[64] H G Graetzer, D. J. Anderson: *The Discovery of Fission. A Documentary History*, Van Nostrand, New York 1971, p. 34-37

[65] Ref [29], p. 58.

[66] Ref [29], p. 54

[67] Ref [22], p. 43

[68] R L Sime, *Am. J. Phys. 58* (1990) 262.

[69] Ref [22], pp. 234ff

[70] J Lemmerich: *Die Geschichte der Entdeckung der Kernspaltung*, Katalog zur Ausstellung in der TU Berlin und im Deutschen Museum München, Universitätsbibliothek Technische Universität Berlin, Berlin 1988, pp 157ff

[71] *Meitner* to *Hahn*, 23 October 1938

[72] I Curie, P Savitch, *J. Phys. Radium 9* (1938) 355

[73] Ref [22], p. 207

[74] *Hahn* to *Meitner*, 25 October 1938.

[75] *Hahn* to *Meitner*, 2 November 1938

[76] *Meitner* to *Hahn*, 4 November (incorrectly dated 4 October) 1938

[77] *Hahn* to *Meitner*, 5/6 November 1938; O Hahn, F. Straßmann, *Naturwissenschaften 26* (1938) 755; submitted on 8 November 1938.

[78] In the same year (1938), when neutron irradiation of thorium produced what appeared to be similar Ra-Ac isomers, *Meitner* calculated (in [62]) that an (n,α) process was possible only with *fast* neutrons

[79] Refs. [41 a] and [41 b], p. 150

[80] O. Hahn, *Naturwiss. Rundsch. 15* (2) (1962) 43; *Hahn* writes "Ihm [Bohr] war die Abspaltung von zwei α-Strahlen aus dem Uran unheimlich. Er konnte sie nicht für möglich halten ..." ("For him [Bohr] the splitting off of two α-particles from uranium was unimaginable. He considered it impossible.") Surely this came from *Meitner* (perhaps *Bohr* also)

[81] Ref. [22], p. 208, note 17

[82] O. Hahn, 1938 Siemens-Taschenkalender, 13 and 14 November 1938 (Archiv zur Geschichte der Max-Planck-Gesellschaft, Berlin-Dahlem), quoted in [83]

[83] P. Brix, *Phys. Bl. 45* (1989) 1

[84] Ref. [6], p. 18, [22], p. 208

[85] Ref. [22], pp. 247 ff

[86] In 1945 (Ref. [29], p. 58) *Hahn* does not give a reason for the fractionation experiment. "Aus irgendwelchen Gründen wollten wir unsere Ra-Isotope etwas anreichern" ("For some reason or other we wanted to enrich our Ra-isotopes somewhat"); later, in Ref. [41 a], pp. 255–256, Ref. [38], p. 20, Ref. [80], etc., he says only that fractionations were needed to detect the weak radiation of a long-lived Ra isomer, a reason *G. Hermann* in Ref. [11 a,b] regards as "rather trivial". More likely, *Hahn* and *Straßmann* were responding to *Meitner*'s request they look for thorium, since if Ra → Ac → Th were true, the resulting Th-231 would be identical or isomeric to the known UY. See *Meitner* to *Hahn*, 26 November and 5 December 1938, abridged in Ref. [22], pp. 250–251

[87] Ref. [22], pp. 104–105

[88] *Hahn* to *Meitner*, 19 December 1938, facsimile in Ref. [70], pp. 166–167

[89] The *Hahn/Straßmann* articles were written by *Hahn* alone. See [6], p. 19, [22], p. 209

[90] O. Hahn, F. Straßmann, *Naturwissenschaften 27* (1939) 11

[91] W. Gerlach: *Ein Forscherleben unserer Zeit*, Oldenbourg, München 1969, p. 53

[92] *Meitner* to *Hahn*, 21 December 1938; facsimile in Ref. [70], p. 171.

[93] According to *E. Bagge*, *Hahn* said in 1945: "Wenn Frl. Meitner im Dezember 1938 noch im Institut gewesen wäre, hätte sie uns das Barium ausgeredet." ("If Frl. Meitner had still been in the institute in December 1938, she would have talked us out of barium.") [Private communication, *R. Fleischmann* to *P. Van Assche*, 1982]; also see *Heisenberg* in [5]. Although such second- and third-hand reports require evaluation of the sources, they are consistent with *Hahn*'s later refusal to include *Meitner* in the discovery

[94] *Hahn* to *Eva von Bahr-Bergius*, 23 December 1938; in [22], p. 267

[95] O. R. Frisch: *What Little I Remember*, Cambridge University Press, Cambridge 1979; pp. 115–117

[96] According to *Fritz Krafft*: "Eine entsprechende Loyalität hätte sie dann eigentlich auch 1938 erwarten können." ("She certainly could have expected a corresponding loyalty in 1938.") See F. Krafft: *Lise Meitner*, Hahn-Meitner-Institut HMI-B448, January 1988 (talk given 2 December 1987.) In their 1918 protactinium paper *Hahn* was even *first* author: O. Hahn, L. Meitner, *Phys. Z. 19* (1918) 257

[97] Even a joint retraction of the transuranes was "vermutlich undurchführbar" because it was politically impossible (perhaps illegal?) for *Meitner* to publish in Germany (*Meitner* to *Hahn*, 1 January 1939); she did not tell *Hahn* details of the Meitner–Frisch interpretation until it was accepted by *Nature* "weil Du ja nicht in der Lage bist, sie unveröffentlicht zu zitieren und weil sie allerlei prüfbare Behauptungen enthält." ("because you are not in a position to cite it before publication, and because it contains a number of (experimentally) provable statements.") (*Meitner* to *Hahn*, 18 January 1939). See also [104]

[98] *Meitner* to *Hahn*, 3 January 1939

[99] *O. R. Frisch* to *Hahn*, 4 January 1939 in [22], p. 271.

[100] *Meitner* to *Hahn*, 18 January 1939

[101] L. Meitner, O. R. Frisch, *Nature (London) 143* (1939) 239

[102] Ref. [29], pp. 64–66

[103] O. Hahn, F. Straßmann, *Naturwissenschaften 27* (1939) 89

[104] *Hahn* also did not acknowledge the suggestion by *Meitner* and *Frisch* of the second fission fragment Kr and its decay products, even though the search for these in Berlin began concurrently or just after receipt of the Meitner–Frisch manuscript. See [22], p. 282–284, and R. L. Sime, *J. Chem. Educ. 66* (1989) 373

[105] *Meitner* to *Walter Meitner*, 6 February 1939

[106] *Meitner* to *Hahn*, 5 February 1939; see *Krafft* in [23] for more on *Meitner*'s conditions in Sweden

[107] Possibly a certain Prof. Krauch (see [29], pp. 64–65) who was pressuring the "politisch belastet" ("politically tainted") Hahn

[108] *Hahn* to *Meitner*, 7 February 1939

[109] *Meitner* to *Hahn*, 2 June 1939, *Hahn* to *Meitner*, 5 June 1939

[110] Ref. [22], pp. 315 ff

[111] *Meitner* to *Hahn*, 12 and 15 July 1939

[112] *Meitner to Max von Laue*, 12 November 1946

[113] In a 1941 review of fission theory, *Meitner*'s once-close associate *C. F. von Weizsäcker* cited everyone except *Meitner* and *Frisch*, see C. F. von Weizsacker, *Forsch. Fortschr. 17* (1941) 10; for *Meitner*'s reaction, see *Meitner* to *Hahn*, 20 January 1941. Also F. Krafft, *Mitt. Österr. Ges. Geschichte Naturwiss. 4* (1984) 1, note 15. The practice of not citing the work of Jewish authors, omitting their names, or attributing their work to others was nearly universal; to my knowledge no attempt has been made since 1945 to correct the record

[114] *Meitner* to *Hahn*, 15 April 1943, citing publications of *Hahn* and *Meitner*, *Fritz Houtermans*, in 1943, substituted *Straßmann*'s name for hers

[115] *Meitner* to *Eva von Bahr-Bergius*, 27 May 1941

[116] O. R. Frisch: "Lise Meitner" in *Dictionary of Scientific Biography*, *Vol. 9*, Scribners, New York 1974, p. 260; Margaret Gowing: *Britain and Atomic Energy 1939–1945*, MacMillan, London 1964, pp. 261 ff., L. Eppstein, Sweden 1988, private communication

[117] *Meitner* to *Eva von Bahr-Bergius*, 21 June 1944

[118] Meitner Diaries: August, September 1945; Churchill College Archives, Cambridge (England).

[119] Ref. [29], p. 72

[120] "Prof. L. Meitner and the splitting of uranium," *Hahn* to Major *Rittner*, Farm Hall, 8 August 1945. *Meitner*'s response, as given in a 1963 interview (Ref. [56], p. 18): "... die Chemiker behaupten ... [daß] wir Physiker solche Prozesse (Fission) für unmöglich erklärt haben, aber wir haben sie ja nie diskutiert ..." ("The chemists claim that we physicists declared such processes (fission) to be impossible, but we in fact never discussed it ...")

[121] *Meitner* to *Eva von Bahr-Bergius*, 30 March 1945

[122] *Meitner* to *Hahn*, 1 April 1946

[123] *Hahn* to *Meitner*, 17 September 1946

[124] *Meitner* to *Hahn*, 20 October 1946

[125] *Meitner* to *Frisch*, 28 November 1946

[126] *Hahn*, [41 a], pp. 208–210; [41 b], pp. 201–203.

[127] *Meitner* to *Eva von Bahr-Bergius*, 24 December 1946

[128] *Meitner* to *James Franck*, 16 January 1947 (incorrectly dated 1946)

[129] *Straßmann* to *Meitner*, 11 November 1947

[130] *Meitner* to *Straßmann*, 21 December 1947, and *Meitner to Hahn*, 6 June 1948

[131] *Meitner* to *Eva von Bahr-Bergius*, 10 January 1948.

[132] Space does not here permit a discussion of the effect of gender inequity upon *Meitner*, but it is unlikely that a male scientist of *Meitner*'s status would be remembered as anyone's *Mitarbeiter*. That *Heisenberg*, who knew *Meitner* very well when she was still in Germany, would refer to her as *Hahn*'s *Mitarbeiterin* and ignore her work probably indicates chauvinism of more than one variety

[133] *Meitner* to *Hahn*, 22 June 1953

[134] *Hahn*, [40 a], p. 86, pp. 147–148

[135] *Meitner* to *Lola Allers*, 29 December 1946

[136] In a very mild response to *Hahn*'s 1962 scientific biography, *Meitner* in 1963 ("Wege und Irrwege zur Kernenergie" [9]) described for the first time her own initiative and noted mistakes in both physics and chemistry, much the same in a 1963 taped interview. Ref. [56]

[137] So stated by *Zimen* in [2]. For "proof" *Zimen* suggests that physicist *Manne Siegbahn* knew *Meitner* personally and would have nominated her for a Nobel Prize had her work deserved it. The suggestion is disingenuous and mean: *Zimen*, who lived in Sweden at the time, surely knows that it was precisely the poor relationship between *Meitner* and *Siegbahn* that *prevented* her from being considered for a Prize. *K. Starke* (*J. Chem. Educ. 56* (1979) 771) is less strident but also ties the discovery to *Meitner*'s absence (which he attributes to her loss of Austrian citizenship!)

[138] In the U.S.A. this was understood; according to *Glenn Seaborg* (personal communication, 1988), *Meitner* was included with *Hahn* and *Straßmann* in the 1966 Enrico Fermi Prize for this reason

[139] P. Levi: *The Drowned and the Saved* (R. Rosenthal, transl.), Vintage International, New York 1989, p. 31

[140] An abbreviated list of recent German contributions: The work of *Fritz Krafft* (Refs. [22, 23, 96]) has had significant influence, *Charlotte Kerner*s's book [24] received the (West) German prize for *Jugendliteratur* in 1987, the comments of *Renate Feyl* [1] have struck a resonant chord, so also the work by *H. Königsdorfer*: *Respektloser Umgang*, Luchterhand, Darmstadt 1986; *Lemmerich*'s 1988–1989 "Ausstellung zur Geschichte der Kernspaltung" [70] included *Meitner* equitably, ceremonies in 1988 and 1989 for the Lise-Meitner-Gymnasium in Böblingen included contributions by *Peter Brix* (Heidelberg) (P. Brix, *MPG-Spiegel* 1/90, p. 29), *Paul Kienle* (GSI Darmstadt) und *Evelies Mayer* (TH Darmstadt)

SOLVAY
SOLVAY
PERFORMANCE CHEMICALS
A DIVISION OF SOLVAY SPECIALTY CHEMICALS, INC.

November 23, 1994

Dr. Alfred Bader
Astor Hotel
Suite 622
924 East Juneau Avenue
Milwaukee, WI 53202

Dear Sir:

Enclosed is a letter describing our offer of three of our product lines to be placed in the Aldrich Chemical Catalog.

They are the High Purity Alkaline Earth Products, Glycerol Compounds and High Temperature Superconductors.

I felt that these would be an excellent addition to the catalog.

Sincerely,

Dr. Rudy Feist
Director of Sales
Specialty Chemical Division

RF/as
Encl.

SOLVAY PERFORMANCE CHEMICALS
41 West Putnam Avenue, Greenwich, CT 06830 (203) 629-7900 Fax: (203) 629-9074

SOLVAY

SOLVAY
PERFORMANCE CHEMICALS
A DIVISION OF SOLVAY SPECIALTY CHEMICALS, INC.

November 23, 1994

Alfonse W. Runquist, Ph.D.
Aldrich Chemical Company, Inc.
1001 West St. Paul Avenue
Milwaukee, WI 53233

Dear Sir:

During our meeting on Monday, October 17 we discussed your interest in adding new products for your catalog. We believe that three of our product lines should be included. The first is our High Purity Alkaline Earth Products: Barium Carbonates, Calcium Carbonates, Strontium Hydroxides, and Strontium Carbonates. These products have been developed for electro ceramic application. They vary in quality from every other product on the market and have been refined especially for electro ceramic application.

A second product line would be the Glycerol Compounds that were specifically developed for the food, pharmaceutical and cosmetic industries. And a third line are the High Temperature Superconductors where we are the leading company worldwide producing these super conductive powders for various applications.

These are three excellent product lines that I would recommend for your catalog. They are top of the line products that would greatly enhance your catalog offerings for you customers. Enclosed is some descriptive information on these three product lines.

I apologize for taking so long to respond but I have had a very heavy travel schedule during the last several weeks. We hope to hear from you soon.

Sincerely,

Dr. Rudi Feist
Director of Sales
Specialty Chemicals Division

RF/as
Encl.

SOLVAY PERFORMANCE CHEMICALS
41 West Putnam Avenue, Greenwich, CT 06830 (203) 629-7900 Fax: (203) 629-9074

SOLVAY
SOLVAY
PERFORMANCE CHEMICALS
A DIVISION OF SOLVAY SPECIALTY CHEMICALS, INC

November 22, 1994

Dr. Alfred Bader
Astor Hotel, Suite 622
924 East Juneau Avenue
Milwaukee, Wisconsin 53202

Dear Dr. Bader:

Please accept my sincere apology for not writing sooner, but my travel schedule for the past few weeks has been unusually heavy. As a followup to our recent discussion concerning SPC's supply of new product groups for Aldrich's catalog business, I will be writing directly to Aldrich shortly with complete information, and will forward a copy to you.

On a more personal note, Petra and I very much enjoyed our day with you. It was a pleasure to chat over lunch, and we were enthralled with our own private tour of your most impressive gallery (we didn't want to leave!). It was interesting to see the paintings depicted on the cover of your catalogs "in the flesh", and while they are a little beyond our budget, we stored up enough visual impressions that day to last a lifetime! We will always remember this delightful visit.

I hope to be in touch with you very soon. Thank you once again for your assistance and your gracious hospitality.

Sincerely,

Dr. Rudi Feist
Director of Sales
Specialty Chemicals Division

SOLVAY PERFORMANCE CHEMICALS
41 West Putnam Avenue, Greenwich, CT 06830 (203) 629-7900 Fax: (203) 629-9074

SOLVAY
SOLVAY
PERFORMANCE CHEMICALS
A DIVISION OF SOLVAY SPECIALTY CHEMICALS, INC

November 23, 1994

Dr. Alfred Bader
Astor Hotel
Suite 622
924 East Juneau Avenue
Milwaukee, WI 53202

Dear Sir:

Enclosed is a letter describing our offer of three of our product lines to be placed in the Aldrich Chemical Catalog.

They are the High Purity Alkaline Earth Products, Glycerol Compounds and High Temperature Superconductors.

I felt that these would be an excellent addition to the catalog.

Sincerely,

Dr. Rudy Feist
Director of Sales
Specialty Chemical Division

RF/as
Encl.

SOLVAY PERFORMANCE CHEMICALS
41 West Putnam Avenue, Greenwich, CT 06830 (203) 629-7900 Fax: (203) 629-9074

SOLVAY
SOLVAY
PERFORMANCE CHEMICALS
A DIVISION OF SOLVAY SPECIALTY CHEMICALS, INC

November 23, 1994

Alfonse W. Runquist, Ph.D.
Aldrich Chemical Company, Inc.
1001 West St. Paul Avenue
Milwaukee, WI 53233

Dear Sir:

During our meeting on Monday, October 17 we discussed your interest in adding new products for your catalog. We believe that three of our product lines should be included. The first is our High Purity Alkaline Earth Products: Barium Carbonates, Calcium Carbonates, Strontium Hydroxides, and Strontium Carbonates. These products have been developed for electro ceramic application. They vary in quality from every other product on the market and have been refined especially for electro ceramic application.

A second product line would be the Glycerol Compounds that were specifically developed for the food, pharmaceutical and cosmetic industries. And a third line are the High Temperature Superconductors where we are the leading company worldwide producing these super conductive powders for various applications.

These are three excellent product lines that I would recommend for your catalog. They are top of the line products that would greatly enhance your catalog offerings for you customers. Enclosed is some descriptive information on these three product lines.

I apologize for taking so long to respond but I have had a very heavy travel schedule during the last several weeks. We hope to hear from you soon.

Sincerely,

Dr. Rudi Feist
Director of Sales
Specialty Chemicals Division

RF/as
Encl.

SOLVAY PERFORMANCE CHEMICALS
41 West Putnam Avenue, Greenwich, CT 06830 (203) 629-7900 Fax: (203) 629-9074

ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

April 20, 1995

Mr. Robert Steyer &
Mr. Robert Manor
St. Louis Post Dispatch
900 North Tucker Blvd.
St. Louis, MO 63101

Dear Messrs. Steyer and Manor:

I enjoyed reading your excellent article about Sigma-Aldrich in last Sunday's Post Dispatch.

The only detail I question is whether selling a call option must be a technique that counts on the company's stock falling. Of course, I very much hoped that the stock would rise so that Queen's University would get the money rather than the unsold stock.

My autobiography, *Adventures of a Chemist Collector*, is now available in England and will be available, I believe, beginning next week, from Library Limited at 7700 Forsyth Blvd. in Clayton. The person in charge is Ms. Mary McCarthy.

Of course, the English publisher, Weidenfeld, has sent a review copy to you, Mr. Manor, but you know how slow book post can be.

I enclose a copy of the cover, the introduction, and the table of contents. Chapters 12 and 13, of course, are primarily St. Louis stories. When you receive your copy of the book, I would very much appreciate your having it reviewed in your pages and then sending me a copy of the review.

When I see you in St. Louis on May 2nd, I will give you copies of all the correspondence between Sigma-Aldrich, myself, and the SEC, and from that, you will see how immensely hard Sigma management worked not to bring my motion to the stockholders. I really don't know why they worked so hard (and, of course, at such high cost) when all I am asking is that the Board of Directors do its job.

Isabel and I plan to attend the annual meeting on Tuesday, May 2nd, and if you have any questions before then or at the meeting, please just let me know.

With all good wishes, I remain,

Yours sincerely,

AB/cw
Enclosure

bc: Mary McCarthy

By Appointment Only
ASTOR HOTEL SUITE 622
924 EAST JUNEAU AVENUE
MILWAUKEE WISCONSIN USA 53202
TEL 414 277-0730 FAX 414 277-0709

ALFRED BADER FINE ARTS

DR. ALFRED BADER
ESTABLISHED 1961

April 13, 1995

Dr. Alfredo Sadler
Sigma-Aldrich Brazil
Rua Sabara, 566-conj. 53
01239-010-Sao Paulo, SP
Brazil

Dear Dr. Sadler:

When I saw the March 1995 Aldrich Reporter, I had to laugh and cry at the same time.

Laugh happily because I saw that you have become Sigma-Aldrich's representative in Brazil, and of course, I remember our long and happy correspondence of some years ago.

Unfortunately, I must have been traveling when you were in Milwaukee, but when you come next, please do let me know in advance and plan to spend an evening with us.

In the meantime, I have completed my autobiography and enclose copies of the Table of Contents, Introduction and cover. Of course, that book will not be available from Aldrich, but you will have no difficulty finding many copies here.

I also had to cry because I realized how parochial our people can be. They have moved Groningen from Holland to Belgium!

With all good wishes, I remain,

Yours sincerely,

AB/cw

By Appointment Only
ASTOR HOTEL SUITE 622
924 EAST JUNEAU AVENUE
MILWAUKEE WISCONSIN USA 53202
TEL 414 277-0730 FAX 414 277-0709

ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

May 10, 1995

Mr. Robert Steyer
St. Louis Post Dispatch
900 North Tucker Blvd.
St. Louis, MO 63101

Dear Mr. Steyer:

Thank you for writing that very fair article about Sigma-Aldrich in your May 3rd issue.

I was not at all surprised that only the owners of 6 million shares voted for my proposal, because I had made practically no effort to convince major shareholders.

What is important, I believe, is that the directors got the message and several analysts have told me that the company is now much more open with information.

The company tried immensely hard to keep this vote from coming before stockholders. I enclose copies of the entire correspondence with the SEC; note the 16-page letter of the Company's lawyer dated January 5, 1995.

I do hope that you have received your copy of my autobiography, *Adventures of a Chemist Collector*, which the publisher sent to Mr. Manor early in April. If you have not received it, I would be happy to send you another copy.

Best personal regards to you and Mr. Manor, as always,

AB/cw

Enclosures

By Appointment Only
ASTOR HOTEL SUITE 622
924 EAST JUNEAU AVENUE
MILWAUKEE WISCONSIN USA 53202
TEL 414 277-0730 FAX 414 277-0709

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

October 17, 1996

Dr. Eugene Shmuylovich
R.W. Johnson Pharmaceutical Research Institute
Route 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Shmuylovich:

I am rather sorry to note from your letter of September 24th that you are leaving J&J, which is surely one of the best companies of its kind in the United States.

There are a number of Russian scientists trying to set up companies to bring interesting compounds made in Russia to the United States, and I fear that you will find a good deal of competition.

Dr. Shmuylovich, please remember that I have never met you personally and know nothing about your work. Originally, I tried hard to help you because your father is a good friend of one of my oldest and best friends in Europe, Dr. Paul Löw-Beer. But please understand that I could not write a letter or recommendation for someone whom I do not know.

All I can do is wish you the best of luck.

Sincerely yours,

AB/cw
bc: Bert van deun
bc: Dr. Paul Löw-Beer (w/encl)

PHARMACEUTICAL RESEARCH INSTITUTE

Sept 24
~~August 28~~,1996

To : Dr. ALFRED BADER
ASTOR HOTEL SUITE 622
924 EAST JUNEAU AVENUE
MILWAUKEE , WISKONSIN 53202

From: EUGENE SHMUYLOVICH

Dear Dr. Alfred Bader :

You probably haven't heard from me for 6 month or so. I have been working for R.W.Johnson PRI. (Johnson & Johnson) since 1990. My work was mainly synthesis of organic compounds for internal use. This work was the part of the major undertaking by J & J to organize the drug discovery organization . I have been with the company for 6 years and I believe that practice and style practiced within RWJ-PRI (and probably in some other major companies) leaves me no opportunity for future.

So, I decided to break away to create my own business.

I have followed new developments in pharmaceutical industry. Major pharmaceutical houses are buying a significant number of compounds from brokerage companies. These suppliers have contracted with the number of chemists all over the world in order to provide the market with millions of synthetic compounds for drug screening and combinatorial chemistry projects.

I plan to establish the brokerage company that will contract with scientists and chemists in Eastern Europe (especially in countries with traditionally strong pharmacological and synthetic chemistry schools) in order to supply compounds for the U.S. market.

Your letter of reference will be the most valuable for establishing such a business, and if you could refer me to the appropriate person or company it would be extremely helpful.
Any advice you could give will be appreciated.

Very truly yours,

Eugene Smuylovich

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

April 26, 1994

Mr. Walter Stern
11710 Lindemere Drive
St. Louis, Missouri 53131

Dear Walter,

I am just completing my autobiography and would very much like to ascertain that the many facts given are correct.

Could you please glance over the enclosed. I heard that story from Dan Broida and hope it is correct.

All good wishes from house to house.

Sincerely,

Enclosure

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

January 7, 1993

Mr. and Mrs. Walter Stern
11710 Lindemere Drive
St. Louis, Missouri 63131

Dear Renata and Walter,

Yours were the only greetings of the season which we received from St. Louis, and as you will be able to imagine, your note gave us a great deal of pleasure.

Do visit us when next you come to Milwaukee, and I will let you know when we visit St. Louis. You, at least, do not have to be worried that you might be fired if you are seen with the Baders.

All good wishes.

Sincerely,

12-12 92

Walter and I came to Milwaukee
in March, here for an Orchestra tour
and had hoped to invite you
to have dinner with us, but
you had left for Europe. This
year only cards.
We want to wish you a Happy
Holiday Season, and a
very Happy New Year - the
world can use it.
With best wishes

Walter & Renate Stern

Reorder from
American Orchid Society—6000 S. Olive Ave.
West Palm Beach, FL 33405
Artwork by Marion R. Sheehan

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

September 16, 1994

Mr. and Mrs. Walter C. Stern
11710 Lindemere Drive
St. Louis, Missouri 63131 4224

Dear Renate and Walter,

Isabel and I appreciated the four hours we spent with you last Sunday, more than we can tell you.

What if--all of the executives at Sigma had had as great a rapport as you and I. But remember, it is difficult to think historically. I do believe that the present regimé will end before very long, and there are so many good people like you at Sigma that the company's great work will continue.

Fond regards.

Sincerely,

Walter & Renate Stern
11710 Lindemere Dr
St.Louis,Mo., 63131
Phone (314) 821-2280

9/7/94

Dear Alfred:

It certainly was wonderful to spend some time with both of you at the airport. As I promised, I am enclosing slides of the pictures and a copy of the notice regarding Ron Wolfe. Unfounded rumors are flying but have no basis in fact.

With best regards from both of us to both of you

Yours Walter

Mr Walter C. Stern
11710 Lindemere Dr
St Louis, MO. 63131-4224

Dr. Alfred Bader
2961 North Shepard Ave.
Milwaukee, Wisconsin
53211

File: Walter Stein
Sigma

May 6, 1996

Dear Alfred:

Thank you for your note. I am sorry we had to miss you.

Before I retired last year, there was some discussion on cutting back on the number of assays that the lab needs to perform. One suggestion was to accept analytical certificates, stating the analytical data and the procedure used to obtain the data - from select suppliers who had been approved by the assay department, based on the past record of reliable service. I do not know if and how this was resolved. Dr. Rodger Izzo, head of Analytical Service Department, may be willing to answer your questions.

I hope all is well with you and Isabel.

Best wishes,
Walter.

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

April 11, 1996

Mr. and Mrs. Walter C. Stern
11710 Lindemere Drive
St. Louis, MO 63131-4224

Dear Renate and Walter,

Southern Illinois University in Edwardsville has invited me to give a number of lectures next week.

The penny just dropped that this is really not far from St. Louis, and if you might like to listen to one or two of these talks, we would, of course, love to see you.

With best wishes from house to house, I remain,

Yours sincerely,

AB/cw

Enclosures

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

April 29, 1996

Mr. Walter C. Stern
11710 Lindemere Drive
St. Louis, MO 63131-4224

Dear Walter:

We had a really fine three days in Edwardsville and were only sorry that you and Renate didn't have a chance to come. Thank you so much for your note.

Quite a few middle management chemists from Sigma came, and several of them mentioned a frightening development. To cut down on expenses, it has now been decided that many purchased products are no longer analyzed at all - not even for identity - and of course that does cut down on costs and back-order lines. Dan Broida would turn around in his grave if he knew of that! I have discussed this with Marvin Klitsner, who agrees that I should send a certified letter to David Harvey with copies to all the directors, pointing out how very hazardous this practice is. But Marvin cautioned me that I should send that letter only if I can make absolutely certain that these facts are correct.

Do you know anything about this?

With all good wishes from house to house, I remain,

Yours sincerely,

AB/cw

April 15, 1996

Dear Alfred:

We just received your note regarding your lectures in Edwardsville, and we are so sorry that this week is completely filled - We are leaving on Thursday, 4/18, for a meeting in Atlanta. We had hoped to make at least one meeting, but it just is not possible and we are very disappointed.

From what I gather there is a new wind blowing at DeKalb, new programs, new people, and increased sales and profits. The last union election must have brought religion to Tom.

We manage to keep busy and hope for Spring. Quite a few perennuals froze this past winter, also one azalea, and some of the roses look doubtful. Peas, spinach, and lettuce are starting to come up (that is Renate, the eager gardener, talking).

I hope that you are all in good health.

Yours sincerely,

Walter

File

Walter
~~Stern~~

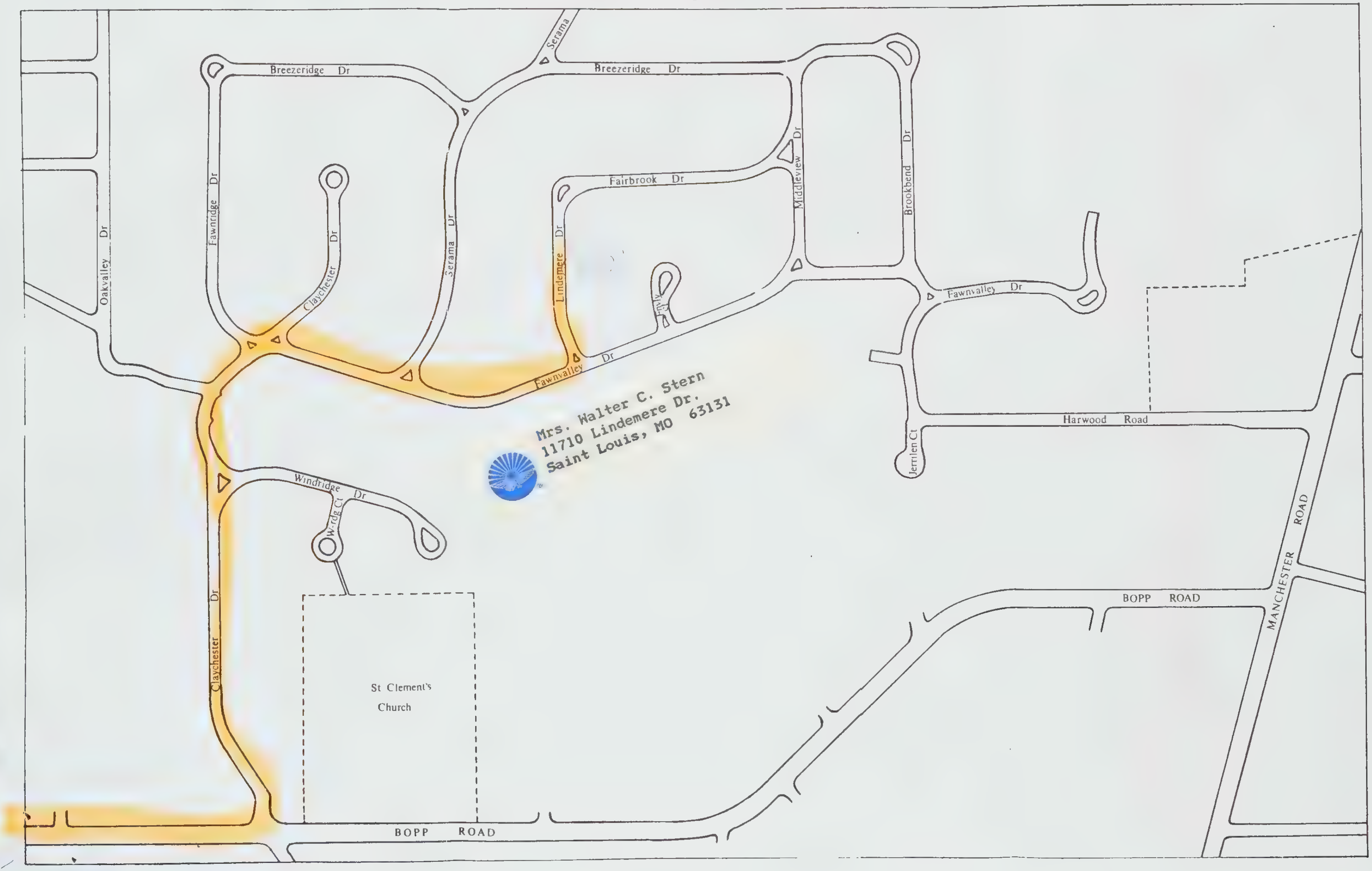
Lindemere is located in Harwood Hills, and you can come in either from Manchester Road: turn north between the Flaming Pit and the Mercantile Bank ~~closed 905 liquor store on~~ Harwood Road, make a curve to the right and ~~follow the double yellow line which leads you~~ into Fawn Valley, and turn right into the third street which is Lindemere. The house is the third on the right; OR if you come from Clayton Road, turn south into Bopp Road for about 1½ miles, turn east into Harwood Hills on Claychester, and ~~follow~~ move to the right after crossing a small bridge th~~e double yellow line~~ (Fawn Valley) to Lindemere which is the second street to the left.

11710 is a 2 story house, the third one from Fawn Valley. It is on the right hand side.

The champagne will be cold

R

HARWOOD HILLS



Mrs. Walter C. Stern
11710 Lindemere Dr.
Saint Louis, MO 63131

Lindemere is located in Harwood Hills, and you can come in either from Manchester Road: turn north between the Flaming Pit and the Mercantile Road ~~closed~~ 905 ~~liquor store on~~ Harwood Road, make a curve to the right and ~~follow the double yellow line which leads you~~ into Fawn Valley, and turn right into the third street which is Lindemere. The house is the third on the right; OR if you come from Clayton Road, turn south into Bopp Road for about 1½ [illegible] miles, turn east into Harwood Hills on Claychester, and ~~follow~~ [illegible] ~~the double yellow line~~ (Fawn Valley) to Lindemere which is the second street to the left.

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

May 3, 1995

Mr. and Mrs. Walter C. Stern
11710 Lindemere Drive
St. Louis, MO 63131-4224

Dear Renate and Walter,

Please accept Isabel's, David's and my sincere thanks for your wonderful hospitality on Monday evening. That chicken dinner was just delicious, but what will always stay in my mind - much more than any dinner, no matter how delicious - is your wonderful encouragement on a human level.

I was so happy to learn yesterday that you are enjoying my autobiography, and I would like to ask you to bring its availability from Library Limited to the attention of as many people at Sigma as possible.

Please also remember that the distance from St. Louis to Milwaukee is exactly the same as that from Milwaukee to St. Louis, and we very much hope to be able to welcome you here soon.

With all good wishes, I remain,

Yours sincerely,

AB/cw

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

August 22, 1996

Mr. Karl-H. Schaper
Der Spiegel
Brandestwiete 19
20457 Hamburg
Germany

Dear Mr. Schaper:

I very much appreciate your sending me the copies of *Der Spiegel* articles dealing with Sigma in 1989 and 1990.

At the time, I was chairman of Sigma-Aldrich in St. Louis and am convinced that Sigma Chemie did not understand at the time that the tiny quantities of toxins sold to Iraq might indeed be misused. And I believe that Sigma Chemie was not fined at the time.

Recently, however, Sigma has made 48 sales, again of tiny quantities, of toxins and this time not to Iraq but mainly to academic institutions in friendly countries. However, U.S. regulations have changed, and these sales require export permits. Sigma was unaware of that and has now been fined $10,000 for each violation, that is, a total of $480,000.

It strikes me as a great deal of money, but the law is the law, and I hope that management in St. Louis has learned a lesson.

Again, with many thanks for your help and best regards, I remain,

Yours sincerely,

AB/cw

August 7, 1996

News Editor
Der Spiegel
Brandestwiete 19
20457 Hamburg
Germany

Dear Sir:

Some five or six years ago, *Der Spiegel* published a detailed story of an American chemical company, Sigma, operating from Sigma in Munich, selling various toxins to Iraq.

As you will see from the enclosed, Sigma has once again sold toxins around the world without U.S. export licenses and hence, Sigma was fined $480,000.

I would very much appreciate it if you could send me a Xerox copy of your article in your magazine describing Sigma's shipments to Iraq some years ago.

You may wonder why I am interested, and so I would like to identify myself: I am the founder of Aldrich and one of the founders of Sigma-Aldrich and the largest individual stockholder in the company. The enclosed review (in German) of my autobiography describes some of my life.

I would like to use your article of some years ago to document to the directors of Sigma-Aldrich the great carelessness by management of the company.

With many thanks for your help and best regards, I remain,

Yours sincerely,

AB/cw

Enclosures

Mit freundlichen Grüßen

15. VIII.

Karl-H. Schaper

DER SPIEGEL
DAS DEUTSCHE NACHRICHTEN-MAGAZIN

SPIEGEL-Verlag
Brandstwiete 19
20457 Hamburg

Telefon (040) 30 07-2426
Fax (040) 30 07-2966
Telex 2162 477

SPIEGEL-
Leser
wissen
mehr!

DER SPIEGEL

SPIEGEL-
Leser
wissen
mehr!

DER SPIEGEL

SPIEGEL-Leser wissen mehr

DER SPIEGEL

File: Spiegel

TRIP/D SPIEGEL-ARCHIV-Dokument 15.08.1996
Base SV8991 Doknr 8962 2. von 2 1. Schirm

DER SPIEGEL 1990: Nr.41 08.10.1990 S.148-152a
ARTIKEL GESCHICHTE-3 Dt. Firmen helfen Irak b. B-Waffen-Herstellung
----

"Wir haben Überraschungen"

Wie deutsche Firmen den Irak für die biologische Kriegführung ausrüsteten

Bei der Firma Labsco GmbH & Co. KG im hessischen Friedberg ging am 14. Mai vergangenen Jahres ein Fernschreiben aus Bagdad ein. Der irakische Geschäftspartner des hessischen Laborausrüsters meldete sich mit dem Absenderkürzel "212202 MIDEF IK".

Das Telex wurde dringend erwartet. Die Hessen hatten auf mißtrauische Rückfragen eines englischen Zulieferers im Irak nachgehakt, was die Araber mit der bestellten Ware anfangen wollten: ein weit über 100 Positionen umfassendes Sortiment aus Seren, Wärmegeräten und Trockenschränken.

Die Erklärung war eindeutig. Bagdad versicherte, daß der Auftrag A-3871 weder "für Versuchszwecke noch zur Produktion von chemisch/biologischen Waffen bestimmt" sei. Die Apparaturen und biologischen Substanzen dienten lediglich "Untersuchungszwecken im klinischen Hospitalbereich".

Daß die Auskunft schlechterdings nicht stimmen konnte, folgt schon aus dem Absender: "MIDEF" ist das Kürzel für das "Ministry of Defense" des kriegerischen irakischen Diktators Saddam Hussein.

Der Auftrag für die westdeutschen Produzenten ist von hohen irakischen Militärs unterzeichnet, die im zynischen Sprachgebrauch der Bagdader Regierung tatsächlich als "Apotheker" firmieren. Die meisten arbeiten denn auch in der Abteilung für chemische Kriegführung.

Zwei sind nach Geheimdienstinformationen sogar Mitarbeiter beim Staatsunternehmen "State Establishment for Pesticides Production" (Sepp). Da läßt Hussein seine weltweit gefürchteten biologischen Waffen herstellen - nach Erkenntnissen der schwedischen Sipri-Friedensforscher "hundertmal tödlicher als die gegenwärtigen C-Kampfstoffe".

Nun spüren Ermittler der hessischen Zollfahndung hinter den Lieferungen aus Friedberg her. Doch wie die biochemischen Ausrüstungen aus der Bestellung A-3871 in Bagdad verwendet wurden, ließ sich vorerst nicht klären.

Die Beweise, daß die Produkte zum Bau von Biowaffen verwendet wurden, liegen, wenn es sie gibt, unerreichbar in Bagdad. In Friedberg stießen die Fahnder allein auf unglaublich naive Beteuerungen der Lieferanten.

"Niemals", sagt Labsco-Geschäftsführer Jürgen Huth, sei ihm bei dem Auftrag (Wert: 1,56 Millionen Mark) der Gedanke gekommen, "daß es sich um eine andere Anwendung als im Hospitalbereich handeln könnte". Das ist für ihn "auch heute nach wie vor schlicht undenkbar". Die Namen der Offiziere kenne er nicht: "Ich kann ja kein Arabisch."

Dabei weiß seit Jahren jeder Fachmann, daß Saddam Husseins Einkäufer weltweit Laborausrüstungen, Bakterienstämme, Nährlösungen und Fermentationsanlagen für die Entwicklung der bakteriologischen Kriegführung zusammenkaufen. Und offenbar sind - nicht anders als bei Atom- und Chemiewaffen - die Deutschen gute Lieferanten.

Ein gutes halbes Dutzend Firmen sind im Visier der Fahnder.

DER SPIEGEL 1990: Nr.41 08.10.1990 S.148-152a
ARTIKEL GESCHICHTE-3 Dt. Firmen helfen Irak b. B-Waffen-Herstellung

---

Schon seit drei Jahren weisen amerikanische Dienste auf verdächtige westdeutsche Unternehmen hin.

Abermals ist auch das Hamburger Unternehmen "Water Engineering Trading" (W.E.T.), das sich bereits mit Giftgasgeschäften einen Namen gemacht hat (siehe Seite 152), in die Affäre verwickelt. Die Firma hat Stoffe, die zur Herstellung von Biowaffen geeignet sind, geliefert.

Informationen deutscher Ermittler über die Beteiligung der Hamburger Gesellschaft an der biologischen Aufrüstung in Bagdad sind schon im vergangenen Jahr in der Bonner Staatssekretärsrunde diskutiert worden. Doch die Beamten reagierten wie gehabt. Mit Rücksicht auf das ohnehin angeschlagene Image der deutschen Industrie wurde die Sache geheimgehalten.

Der Deal mit W.E.T. lief über die irakische Sepp, die Brutschränke und Nährböden bei den guten Bekannten aus der Hansestadt orderte. Der W.E.T.-Manager Peter Leifer ließ die Apparaturen bei einer Firma in Hannover besorgen, die wichtigeren Nähr-Substanzen wurden bei der damaligen Oxoid GmbH, heute Unipath GmbH, in Wesel am Niederrhein bestellt. Die Firma unterhält einen Großhandel für bakteriologische Nährböden.

W.E.T. orderte 48 ungeimpfte Fermente, mit denen sich nach einigen Behandlungen beispielsweise Pesterreger züchten lassen.

--- S.149

Dem ahnungslosen Weseler Oxoid-Geschäftsführer Georg Füllbrunn wurde mitgeteilt, es handele sich um eine Lieferung nach Nigeria. Füllbrunn: "Von Irak haben die nichts gesagt."

Die Lieferungen aus Hamburg sind mit schuld daran, daß Hussein nun mit einem Arsenal von biologischen Waffen die ganze Welt in Angst versetzen kann.

Nach amerikanischen Geheimdienstberichten, die in der vorletzten Woche dem US-Repräsentantenhaus vorgelegt wurden, kann der potentielle Kriegsgegner Irak möglicherweise schon Anfang nächsten Jahres eine beträchtliche Zahl biologischer Waffen einsetzen. Dazu gehöre der Virus Anthrax, der lebensgefährliche Blutungen hervorrufen kann. Schon prahlt der irakische General Mondher Abdel Rahman, der Irak habe "noch große und wirkungsvolle Überraschungen für die Amerikaner".

Das Potential des Despoten ist jetzt schon ansehnlich. Vor fast zwei Jahren meldete der Geheimdienst CIA, der Irak produziere das hochwirksame Lebensmittelgift Botulinus-Toxin in großen Mengen.

Mit Erfolg wurden offenbar in den B-Waffenlabors Stoffe entwickelt, die Pest, Cholera, Milzbrand oder Typhus auslösen können. Die Bakterien können in Sprengköpfe gefüllt oder vom Flugzeug aus versprüht werden. Möglich ist auch, die Viren über Wirtstiere wie Zecken auf den Menschen zu übertragen.

Die irakischen B-Waffenlabors sind, anders als die Giftgasküchen, nicht mit Satellitenfotos zu erfassen. Sie sind uneinsehbar in Bunkern untergebracht.

(* Demonstration der)
(Probeentnahme-Vorrichtung für Einsätze)
(in verseuchten Gebieten.)

Trotzdem wurden die irakischen Seuchen-Anlagen geortet. Sie stehen, geschützt von einem dichten Raketengürtel, in Salman Pak, 35 Kilometer südostwärts von Bagdad, und in Samarra, über 100 Kilometer

DER SPIEGEL 1990: Nr.41 08.10.1990 S.148-152a
ARTIKEL GESCHICHTE-3 Dt. Firmen helfen Irak b. B-Waffen-Herstellung
----

nördlich der Hauptstadt - neben den C-Waffen-Anlagen, die dort die Dreieicher Firma Pilot Plant errichten half.

Die US-Geheimdienste vermuten, daß das wissenschaftliche Interesse der irakischen B-Waffenforschung in letzter Zeit immer mehr den Pilzgiften, sogenannten Mykotoxinen, gilt. Vor allem die zu den Trichothecenen zählenden Wirkstoffe HT-2 und T-2 sind begehrt.

Auch für die Ausrüstung mit Pilzgiften waren die Deutschen eine gute Adresse. Lieferant war ein Josef Kühn aus dem niedersächsischen Neustadt am Rübenberge.

Der Kaufmann hat 1986 jeweils rund 100 Milligramm der Mykotoxine T-2 und HT-2 an Bagdad vermittelt. Die von der Oberhachinger Firma Sigma Chemie entwickelten Toxine lösen selbst in starker Verdünnung beim Menschen Krebs aus. Diese Stoffe sind noch in geringsten Mengen wirksam, dazu hitzebeständig und können schon durch Hautkontakt oder Einatmen den Tod bewirken.

Der Mykotoxin-Export, den deutsche Fahnder 1987 aufdeckten, hatte keine rechtlichen Folgen. Die Ausfuhr kleinerer Mengen unterlag nach einem vom Generalbundesanwalt eingeholten Gutachten nicht dem Verbot durch das Kriegswaffenkontroll- oder Außenwirtschaftsgesetz.

Auch die Nährböden-Lieferung von W.E.T. und die zahlreichen Lieferungen von Labsco waren genehmigungsfrei.

--- S.152

Erst seit dem 1. Januar 1990 gibt es eine Ausfuhrliste für sensitive Güter im B-Waffenbereich.

Zudem ist - wie im Fall Labsco - für deutsche Fahnder allzuoft nicht aufklärbar, was mit verdächtigen Bio-Lieferungen an den Irak geschieht.

So machte das amerikanische FBI immer wieder auf eine kleine Firma in Köln aufmerksam, die sich durch häufigen Geschäftsführer- und Bürowechsel auszeichnet und einen gar nicht so seltenen Handelszweck hat. Sie exportiert "Gegenstände aller Art, soweit hierzu nicht eine besondere Genehmigung erforderlich ist".

Bundeskriminalamt und Beamte des Kölner Zollkriminalinstituts leiteten Vorermittlungen ein, doch herausgekommen ist bislang nichts. Der Bundesnachrichtendienst nahm Kontakt mit Behörden in Übersee auf, denn eine Firma gleichen Namens gilt dort als Frontorganisation der Irakis.

Oft sind medizinische und militärische Forschung gar nicht voneinander zu trennen. "Gut und Böse", sagt Ralf Schrank, Prokurist beim renommierten Hanauer Gerätehersteller Heraeus, "liegen bei der biologischen Labor-Arbeit eng beieinander."

Ein Heraeus-Rohrofen vom Typ RO 4/25, der auf Temperaturen bis 1100 Grad erhitzt werden kann, wurde beispielsweise 1985 über die Friedberger Labsco in den Irak geliefert. Er eignet sich zur Durchführung chemischer Reaktionen, mit ihm können aber auch, wenngleich nicht sauber, hochtoxische Substanzen verbrannt werden.

Der Rohrofen-Auftrag kam von der Uni Bagdad - doch was heißt das schon. In einem Staat wie dem Irak, sagt der B-Waffen-Experte Oliver Thränert, "gibt es keine eindeutige Trennung zwischen Verteidigungsministerium und zivilen Einrichtungen". Nach dem Kauf werde die Ware womöglich "ans Verteidigungsministerium oder an die Militärs weitergegeben".

Wenn die Militärs, wie angedroht, demnächst im Konflikt am Golf

---

DER SPIEGEL 1990: Nr.41 08.10.1990 S.148-152a
ARTIKEL GESCHICHTE-3 Dt. Firmen helfen Irak b. B-Waffen-Herstellung

---

zu Pest-Bomben greifen sollten, sind die Amerikaner schlecht gerüstet. So fehlen auf den Kampfschiffen am Golf Überdruckgeräte ("positive air pressure"), mit denen nach Bomben-Angriffen die biologischen Kampfstoffe aufs Meer weggeblasen werden könnten. Der Einsatz von B-Waffen würde nach Ansicht von Experten sogar die großen amerikanischen Flugzeugträger verwundbar machen.

Tauglich ist im Bio-Krieg aber ein Panzer, von dem bereits mehr als zehn Exemplare für US-Soldaten in der Wüste bereitstehen. Der Panzer "Fuchs" ist mit Spür-Sensoren ausgerüstet und für jeden B-Einsatz gewappnet.

Er ist ebenfalls ein deutsches Produkt.

Bildunterschriften:
--- S.148
Irak-Exportfirma Labsco: Serum für Husseins Apotheker

Irak-Telex an Labsco (Ausriß): Auftrag vom Kriegsministerium

--- S.149
Deutscher ABC-Spürpanzer "Fuchs"*: Drohung mit Pest-Bomben

Fußnoten:
--- S.149
* Demonstration der Probeentnahme-Vorrichtung für Einsätze in verseuchten Gebieten.

***

*****

DER SPIEGEL 1989: Nr.5 30.01.1989 S.16-18a

ARTIKEL Irak entwickelt B-Waffen mit deutscher Hilfe

"Hundertemal tödlicher als C-Waffen" Mit deutscher Hilfe erforscht und entwickelt der Irak biologische Waffen. Der Bundesnachrichtendienst hat jetzt bestätigt, was zuvor Regierungssprecher Friedhelm Ost verschleiern wollte: Auf Vermittlung eines niedersächsischen Kaufmanns lieferte ein bayrisches Unternehmen aus der Nähe von München Proben hochgiftiger Mykotoxine, die nach Meinung von Experten speziell für Sabotage- und Terroranschläge geeignet sind.

Die Abgeordneten der Parlamentarischen Kontrollkommission (PKK), des geheimen Bundestagsgremiums zur Überwachung der bundesdeutschen Geheimdienste, erlebten am vorigen Mittwoch eine Überraschung. Als seien sie ein Herz und eine Seele, präsentierten sich Staatssekretär Waldemar Schreckenberger, der Geheimdienst-Koordinator des Bundeskanzleramtes, und Hans-Georg Wieck, Präsident des Bundesnachrichtendienstes (BND), den Volksvertretern.

Keine Spur mehr vom Zerwürfnis zwischen dem Bonner Aktenliebhaber und seinem eigenwilligen Pullacher Untergebenen, das angeblich mit dem baldigen Rausschmiß Wiecks enden sollte (Seite 18). Grund der neuen Harmonie: Beide Herren hatten mehr zu verheimlichen, als zu offenbaren. Nur gemeinsam ließen sich Versagen und Mißmanagement westdeutscher Regierungsstellen und Behörden im Skandal um bundesdeutsche Geschäfte mit den auf biologische (B) und chemische (C) Waffen erpichten Staaten Libyen und Irak verbergen.

Das Zweckbündnis bewährte sich, als es galt, in der PKK-Sitzung spezielle Fragen des SPD-Abgeordneten Willfried Penner nach Verstrickungen bundesdeutscher Firmen in die B-Waffenrüstung des Iraks abzuwehren. Schreckenberger, von Wieck unterstützt, wiegelte ab: Nichts Genaues wisse man nicht.

Wohl gebe es, so der Staatssekretär, "eine begründete Vermutung", daß der Irak 35 Kilometer südostwärts von Bagdad in Salman Pak eine B-Waffenanlage betreibe. Ob bundesdeutsche Firmen Anteil hätten "an einer Anlage zur Forschung, Entwicklung oder Produktion von B-Waffen, kann zur Zeit nicht eindeutig
--- S.17
beantwortet werden", weil es "Lieferungen von Produkten gibt, die Mehrzweckcharakter haben, die wir aber nicht klar zuordnen können".

Jedenfalls handle es sich, fügte Schreckenberger hinzu, um Gift-Lieferungen von "marginaler Bedeutung". Es seien derart geringe Mengen in den Irak gegangen, "daß sie nicht für eine bakteriologische Kampfführung" ausgereicht hätten, "allenfalls für wissenschaftliche Forschungs- und Laborzwecke".

Genau darum ging es. Daß der Irak zu bakteriologischer Kriegführung noch nicht imstande ist, weiß zumindest BND-Wieck ganz genau. Doch der Golfstaat ist emsig mit B-Waffen-Forschung und -entwicklung beschäftigt und besonders an B-Waffen-geeigneten Pilz-Giften (Mykotoxinen) interessiert. Die wurden aus der Bundesrepublik geliefert.

Wieck verschwieg vor der PKK auch, daß der BND schon seit längerem von der Gift-Fracht weiß, darüber aber nicht sogleich dem Kanzleramt berichtet hatte. Meldung machte der Dienst erst jetzt während des weltweiten Aufruhrs über die deutschen Lieferungen an Libyen.

DER SPIEGEL 1989: Nr.5 30.01.1989 S.16-18a

ARTIKEL Irak entwickelt B-Waffen mit deutscher Hilfe

Um die Jahreswende 1985/86 hatte der Irak, schwer bedrängt vom Kriegsgegner Iran und bereits erfahren im Einsatz chemischer Kampfstoffe, ein besonders dringliches Anliegen. Regierungsstellen in Bagdad versuchten im westlichen Ausland Mykotoxine zu erwerben; jene äußerst wirksamen Gifte von Pilzen und Schimmelpilzen werden für Forschungen auf dem Gebiet der Nahrungsmittel-Vorratshaltung gebraucht - oder aber für Experimente zur biologischen Kriegführung.

Der BND berichtete jetzt von Informationen, "wonach im Irak Forschungstätigkeiten auf dem Gebiete der B-Waffen durchgeführt werden". Regierungssprecher Friedhelm Ost ergänzte, es gebe auch "vereinzelte Hinweise", daß "die Produktion aufgenommen worden sein könnte". Eine abschließende Wertung sei nicht möglich, auch sei über eine Beteiligung deutscher Wissenschaftler oder Techniker "im Zusammenhang mit den erwähnten Informationen" nichts bekanntgeworden.

Einiges darüber, wie bundesdeutsche Kaufleute und Wissenschaftler in den Zusammenhang mit mesopotamischer Waffenforschung geraten sind, wird gerade bekannt. Bei der Suche der Iraker nach Mykotoxinen hatte sich ein älterer Kontakt Bagdads ins niedersächsische Neustadt am Rübenberge als hilfreich erwiesen. Dort geht der jetzt 40jährige Josef Kühn mit der Firma Plato-Kühn vielfältigen Exportgeschäften nach. 1986 vermittelte Kühn dem Irak einen gewünschten Gift-Lieferanten, die in Oberhaching bei München ansässige Firma Sigma Chemie, spezialisiert auf Lieferungen von Bio-Chemikalien für Forschungsinstitute und deutsche Tochter der US-Firma Sigma in St. Louis. 1987 dann - unklare Zahlungsmodalitäten hatten den Deal verzögert - ging das Gift, als Gefahrengut deklariert, von Hannover per Luftfracht nach Bagdad.

Weder der bundesdeutsche Zoll noch das Bundesamt für Wirtschaft hatten Einwände, weil es sich um sehr kleine Mengen gehandelt habe. Zum Preis von knapp 60 000 Mark erhielt der Irak 100 Milligramm des Mykotoxins HT-2 und über 100 Milligramm des Mykotoxins T-2. Kühn gibt heute an, er wisse auch nicht, wofür die Iraker das Gift gebraucht hätten; es sei immer von "Analysen" die Rede gewesen.

Präziser war der BND: Auch aus diesen geringen Mengen habe der Irak Nutzen ziehen können; die "Verwendung im Rahmen einer eigenen B-Waffen-Forschung, unter anderem bei Tierversuchen", sei möglich gewesen.

Die zu den Trichothecenen zählenden Wirkstoffe HT-2 und T-2 sind seit den sechziger Jahren für B-Waffenforscher von besonderem Interesse. Anders als in früheren Zeiten, als in B-Waffenlabors mit lebenden Erregern von Pest, Cholera, Milzbrand oder Typhus experimentiert wurde, halten Militärs die von Organismen wie Schimmelpilzen produzierten Gifte HT-2 und T-2 für wirksamer.

Das Stockholmer Sipri-Friedensforschungsinstitut stellte fest, Toxine ließen sich so entwickeln, daß sie "hundertemal tödlicher" seien als die gegenwärtigen C-Kampfstoffe. Theodore Gold, bis Mitte
--- S.18
der achtziger Jahre Chef der chemischen Waffenprogramme des Pentagon, glaubt, biologische Waffen würden - nicht zuletzt wegen ihrer raschen Wirkung - in Form von Mykotoxinen entwickelt.

Über die aus der Bundesrepublik an den Irak gelieferten Mykotoxine heißt es bei Sipri, Erkrankungen oder Tod könnten durch Hautkontakt, Einatmen oder orale Aufnahme bewirkt werden.

DER SPIEGEL 1989: Nr.5 30.01.1989 S.16-18a

ARTIKEL Irak entwickelt B-Waffen mit deutscher Hilfe

Mykotoxine, in geringsten Mengen hochwirksam, dazu hitzebeständig, können nur schwierig entdeckt, identifiziert und unschädlich gemacht werden. Die von den Giften ausgelösten Erkrankungen lassen sich schwer diagnostizieren und behandeln. Die Toxine eignen sich laut Sipri besonders gut für Sabotageeinsätze und, so die Furcht von Experten, für Terroranschläge.

Letzte Woche legte der BND nach: Die aus der Bundesrepublik an die Araber gelieferten Gifte hätten bei Tierversuchen tödlich gewirkt, selbst bei starker Verdünnung könnten sie beim Menschen noch Krebs auslösen.

Der Geheimdienst hatte mehr zufällig von der Gift-Lieferung erfahren. Exportkaufmann Kühn war nach anonymen Hinweisen am 30. September 1987 wegen des Verdachts verhaftet worden, Agent des irakischen militärischen Nachrichtendienstes zu sein. Ihm wurde unter anderem zur Last gelegt, für den Irak in Europa bei Piloten Erkundigungen angestellt zu haben, die sich beim Kriegsgegner Iran verdingen wollten.

Während der Vernehmungen - Kühn saß bis Mitte Dezember 1987 in Untersuchungshaft - rückte der Geschäftsmann mit den Angaben über die Mykotoxine-Lieferungen heraus. Bestraft wurde Kühn deshalb nicht. Das Ermittlungsverfahren wegen der angeblichen Geheimdiensttätigkeit für Bagdad stellte die Staatsanwaltschaft gegen eine Geldbuße in Höhe von 25 000 Mark ein.

Der BND, ebenso wie das Bundeskriminalamt seit längerem über den Verkauf der Mykotoxine informiert, berichtete im Januar dem Kanzleramt über den Fall, meldete aber versehentlich eine "Verurteilung" Kühns. Die zuständige Abteilung machte daraus eine "rechtskräftige Verurteilung", von der Regierungssprecher Ost öffentlich redete.

Anderntags widerrief Ost: Die zur B-Waffen-Diskussion gemachten Angaben über die Verurteilung eines deutschen Staatsbürgers seien nicht zutreffend: "Sie gingen auf eine unrichtige Information durch den Bundesnachrichtendienstes zurück."

Doppelter Zweck des Dementis: Der wegen eigenmächtiger Informationspolitik bei Kanzler Helmut Kohl in Ungnade gefallene BND sollte getunkt werden, die Öffentlichkeit den Eindruck erhalten, als wäre an der Lieferung von Mykotoxinen aus der Bundesrepublik an den Irak nichts dran.

--- S.16

Bildunterschriften:

--- S.16

BND-Kontrolleur Schreckenberger, BND-Chef Wieck: "Nur für Forschungszwecke"

--- S.17

Mykotoxin-Lieferant Sigma: Luftfracht nach Bagdad

Firmenschild des Irak-Partners Plato Gift-Kontakt vermittelt

***

*****

Syncrude
Edmonton Research Center

Jean Cooley, Ph.D.
Research Associate

home 446 0795

Syncrude Canada Ltd.
Edmonton Research Center
9421 - 17 Avenue
Edmonton, Alberta T6N 1H4
Tel: (403) 970-6934 Fax: (403) 970-6805

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

August 8, 1994

Dr. Jean Cooley
Research Associate
Syncrude Canada Ltd.
Edmonton Research Center
10120 - 17th Street
Edmonton, Alberta
Canada T6P 1V8

Via Fax 403 449 2805

Dear Dr. Cooley:

I am happy to know from your fax of August 4th that April 10th and 11th are satisfactory for several talks in Edmonton. Of course, the frosting on the cake will be spending some time with Magda and Norman Jones, who guided me into chemical research back in 1945.

By next April my autobiography, *The Adventures of a Chemist-Collector*, should be out and some chemists in Edmonton might be interested in it.

The talk on Richard Anschütz is not just for chemists, but also deals with ethics and physics, and is almost as much a detective story as a scientific one.

I am not sure if I have mentioned this before: I do not demand honoraria from universities, but do expect that travel expenses for Isabel and me be reimbursed. However, they should not be very high as they will be shared, and you might like to put a cap on them and let us know what it is.

What would hurt is if you ask me to give only one talk a day. Two is fine, and three even better. Once I tried to give four, and that was too many.

Sincerely,

c: Prof. Edward Piers

Syncrude
[illegible]
[illegible]
[illegible]
[illegible]

Fax No. (403) 449-2005

[illegible] [illegible]
[illegible] [illegible] Fine Arts
[illegible]
[illegible] [illegible]

[illegible] [illegible]
[illegible] [illegible] Canada Ltd
[illegible] [illegible]
[illegible] [illegible]

[illegible] [illegible]
[illegible]
[illegible] 3

[illegible]

ANY PROBLEMS PLEASE CALL FAX OPERATOR (403) 449-2955

[illegible] [illegible]

75th CSC Conference Lecture Series

A[illegible]

[illegible]

[illegible] Your kind offer to give two or three [illegible] ...ities that we were having in selecting [illegible] ...s of interest to us. I am confident that [illegible] community. We will let you know the [illegible] committee members have returned from [illegible]

The 75th CSC Lecture [illegible] which are solely to pay the expenses for our [illegible]. It [illegible] costs associated with your travel. The University of Alberta Chemistry Department has agreed to cover some of your expenses. Therefore, for the Edmonton portion of your trip and the travel to and from Edmonton the expenses for you and Mrs. Bader will be reimbursed. When it comes time to make the travel arrangements we can decide the best way to accomplish this.

I am certain many of my colleagues will be interested in your autobiography. We have read several articles about you recently - the article in C&E News as well as a recent newspaper article talking about your thoughtful donation to Queen's University.

Sincerely,

Sam [illegible]

cc: Ron Kostecky
Gary Termansen
75th CSC Lecture Series Committee
Edward Piers

FAX FROM

DR. ALFRED R. BADER
Suite 622
924 East Juneau Avenue
Milwaukee, Wisconsin 53202
Telephone 414-277-0730
Fax No. 414-277-0709

January 4, 1995

To: Dr. Jean Cooley and Dr. Robert Cowles
Syncrude - 403 970 6805

Dear Dr. Cooley and Dr. Cowles:

A long trip to Europe has delayed my thanking you for Dr. Cooley's detailed fax of November 30th.

If it is all right with you, Isabel and I plan to arrive in Edmonton from Vancouver on Sunday the 9th and leave on Wednesday morning, April 12th. That would give us ample time for the talks and meeting our best friends in Edmonton.

There is a considerable overlap between the two talks, one on Josef Loschmidt and the other on Richard Anschütz. Hence, it might be better to schedule only one, namely, the one of Loschmidt, and I would include a good deal about Anschütz in that talk.

May I suggest the following:

Monday morning in the Chemistry Department: Josef Loschmidt
Monday evening in the art gallery: The Adventures of a Chemist Collector

Tuesday morning in the Chemistry Department: The History of Aldrich Chemical Co.
Tuesday evening at King's University College: The Bible through Dutch Eyes. Incidentally, this talk can be subtitled "Rembrandt and the Jews" and you might like to invite members of the Jewish community to attend.

If at all possible, we would like to meet with Professor and Mrs. R. Norman Jones, and if he is in Edmonton with Dr. Jerry Terzakian.

All good wishes.

Sincerely,

Alfred Bader

Gilbert Stork

With this *Special Issue*, Synlett initiates a series, to appear intermittently, to honor scientists who have enriched the field of synthetic organic chemistry. We are delighted to dedicate this inaugural issue to Professor Gilbert Stork and are grateful to his former students and collaborators (former members of "The Stork Group") whose thirty-six contributions in honor of their mentor grace these pages.

Gilbert Stork's influence on the logic and practice of organic Chemistry can be traced to the year 1945 when he reported, as the sole author, a synthesis of 3,4-diaminocarbethoxyfuran (the compound was envisioned as a starting material for a planned stereoselective synthesis of biotin). Several generations of synthetic chemists grew up with Stork chemistry and proceeded into their professional lives with permanent imprints of his publications, seminar presentations, and personal "brain storming" from which emerged unique and key insights in methodology and striking applications to complex targets. For instance, Gilbert Stork first described the trapping of enolates from "Birch" reduction of enones, and the regiospecific generation of enolates from silyl enol ethers. His inventive use of enamines and metalloenamines for functionalizing the α-position of ketones and even aldehydes permanently changed the way chemists think about this common synthetic maneuver. Stork himself made brilliant use of this method in the syntheses of alkaloids such as aspidospermine. Advances occasioned by the conception of carbonyl-induced hydration of acetylenes, as well as a host of functional methyl vinyl ketone equivalents (each with a particularly apt function) for Robinson annulations are now standard tools of the trade, with particular application to steroids and other polycyclic isoprenoids. The list goes on and on- protected cyanohydrins as acyl anion equivalents, anionic epoxynitrile cyclizations, and reductive cyclizations of acetylenic ketones. More recently, Gilbert Stork more than any other chemist, was responsible for demonstrating the power of radical cyclizations in synthesis.

To the foregoing incomplete list of synthetic accomplishments must be added the brilliant formulation of the stereochemistry of polyene cyclization (Stork–Eschenmoser hypothesis), an early and fundamental advance in the bioorganic chemistry of triterpenes and steroids. Extensions of Stork chemistry resonate in the literature from 1945 to the present. Indeed, there is no one "Stork Reaction." There are many! Gilbert Stork has, for 50 years, brought new concepts and perceptions to enliven and advance the discipline and the devotees of synthetic chemistry.

Throughout his scientific life, Gilbert Stork has interwoven total synthesis (including that of cantharadin, the first stereospecific construction of a complex natural product) and mechanistic studies for the purpose of his true love, that of inventing and developing new methods to attain positional- and stereospecificity.

In the course of these demanding pursuits, he also sets an admirable model of professional and humanistic behavior. From insecure graduate student to industrial executive, all have gained and continue to gain from his generous advice, his recognition and his encouragement. In interactions, be it with students or members of lecture audiences, Gilbert Stork extends his undivided attention and creates an atmosphere for friendly and engaging discussion. Such discussions, which start with synthetic chemistry can range far and wide (and may even get around to vintage automobiles, one of his secondary passions).[1] His scientific accomplishments and character constitute a living legacy and an inspiration to our community.

The quintessence of Gilbert Stork emerges, perhaps, in the following credo. "I truly believe that synthesis is tremendously important for the progress of organic chemistry. One cannot be interested in a method merely in an abstract way; the scope and limitations of a method can be best explored by applying it under difficult and preset requirements - and that is "synthesis."[2]

On behalf of the "The Stork Group," the numerous colleagues and friends, and the greater synthetic community, we wish Gilbert continuing creative and productive paths in synthetic chemistry. His visions in science continue to expand our horizons, through both the written and the oral word.

Samuel J. Danishefsky, Clayton H. Heathcock, Guest Editors

Victor Snieckus, Editor, The American continents[3]

---

[1] See the warm and witty account, "Gilbert Stork. A Celebration of 35 years in Research & Teaching" by Hoffman, F. Alrichim. Acta **1982**, *15*, 3.

[2] Schmalz, P. Organische Synthese - Zukunft und Gegenwart, Nachr. Chem. Tech. Lab. **1987**, *35*, 349.

[3] Victor Snieckus expresses his gratitude to Barb Weber for uncompromising attention to the achievement of this Special Issue.

75th CSC Conference Lectures

November 30, 1994

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin, USA
53211

Dear Dr. Bader

I have circulated your list of talks to a number of chemists in the Edmonton area. For the chemistry ones the preferred ranking is
History of the Aldrich Chemical Co.
Josef Loschmidt --The Father of Molecular Modelling
Richard Anschutz: Acts of Atonement
For the public lectures the preferred ranking is
The Adventures of a Chemist Collector
The Bible through Dutch Eyes
Most people expressed interest in any of the talks and found it very hard to rank them.

I have tried to work out a schedule of presentations which will allow us to hear a number of talks, allow you time to visit with your friends here and also allow some time for other activities. This is the first draft and I hope you will comment on it so we can improve it.

On Monday we propose a chemistry lecture, either the Josef Loschmidt or the Richard Anschutz presentation, at the University of Alberta Chemistry Department at 11:00 am. This is the time for regularly scheduled seminars in the Department so it will be convenient for many University of Alberta chemists.

We propose that the "History of the Aldrich Chemical Company" be given at the University of Alberta Chemistry Department at 4:00 pm on Monday. By having it late in the afternoon we feel that in addition to University of Alberta staff and students it will be possible to attract attendees from industry and government labs.

On Monday evening we propose having a public lecture, "The Adventures of a Chemist Collector", at the Art Gallery. I have discussed this with the Executive Director of the Art Gallery and he is excited about this possibility. He will open the Art Gallery that evening for us (it is not normally open on Monday evenings) and he will waive the normal admission charge. He has suggested that we allow some time prior to your lecture during which we can visit the gallery (7:00 to 8:00 pm). This would be followed by your lecture and we would have coffee and informal conversations afterwards. If this aspect of your visit could be finalized by the end of the month he would be able to begin advertising it in the art community in his late December mailings. This should be an excellent opportunity for chemists and the art community to meet.

On Tuesday we propose that the third chemistry lecture be given at the University of Alberta Chemistry Department at 11:00 am.

If you are still here on Tuesday evening and we hope that you will be, we would like you to present "The Bible Through Dutch Eyes" at The King's University College. This is a small Christian private University which was founded by Dutch Immigrants many years ago. Therefore, we expect to attract chemists as well as Bible students and the Dutch community to this talk. The University relocated about two years ago and they have good auditorium facilities as well as residences for their students. Previous functions which we have held there have been very successful.

The above is a draft. We have scheduled the number of talks bearing in mind that you wish to give two or three talks per day. There is still flexibility in the schedule.

Since my last correspondence with you Syncrude Research has moved into a new facility in a Research Park. Our new address is
Syncrude Canada Ltd.
Edmonton Research Center
9421 - 17 Avenue
Edmonton, Alberta
T6N 1H4
My new phone number is 403-970-6934 and the new fax number is 403-970-6805.

We have had a very successful season of local chemistry meetings this year and we are looking forward to your visit in 1995.

Sincerely

Jean cooley

Jean Cooley

cc. 75th CSC Conference Lecture Committee
B. Kratochvil
A. Bogusky (Art Gallery)

FAX FROM

DR. ALFRED BADER
Suite 622
924 East Juneau Avenue
Milwaukee, Wisconsin 53202
Telephone: 414/277-0730
Fax: 414/277-0709

March 22, 1996

To: Dr. Jean Cooley
Syncrude Canada Ltd.
Fax: 403/970-6805

Dear Dr. Cooley:

I am particularly happy to have your fax of yesterday because I simply couldn't understand how a letter mailed to you, at one of Edmonton's most famous companies, would simply be returned to me.

I am glad that Norman Jones will review my autobiography. It was really he who got me excited about chemical research. Could you perhaps suggest that the article mention that the book is available both from Queen's University and from Little, Brown in Toronto?

May I ask you for your opinion about a totally different matter? A good friend of mine in Canada has told me that there is a totally new technology to extract oil from the Alaska tar-sands. This technology has been developed over a number of years by a company called Solv-Ex and that a Canadian company, UTS, traded on the Toronto Stock Exchange, had an interest in Solv-Ex.

I have not yet seen the underlying patents for this technology, but I feel confident that as Syncrude is the biggest extractor of oil from the Alberta tar-sands, you will know a good deal about this new technology. Is this just a pipe-dream, or do you think that it will become reality?

I still remember with such pleasure our happy days in Edmonton last April - happy, of course, largely because of your gracious hospitality.

With all good wishes, I remain,

Yours sincerely,

AB/cw

Syncrude
Edmonton Research Center
9421 - 17 Aven
Edmonton AB
T6N 1H4
403) 970 68

Fax No. (403) 970-6805

To: Dr. Alfred Bader
Company:
Phone:
Fax: 414-277-0709

From: Jean Cooley
Company: Syncrude Canada Ltd
Phone: 403-970-6934
Fax: 403-970-6805

Date: 03.21.96
Pages including this cover page:

Comments:

Dr. Bader

Thank you for your kind letter earlier this year. Yes, I did receive it. Syncrude Research was located on 17 Street for about 25 years. We had an old warehouse which we kept modifying to suit our needs. Finally about a year ago we moved to 17 Avenue and into the Edmonton Research Park. I'm sorry the post office did not forward your letter but rather returned it to you. Our new address is at the top of the page.

The other day I contacted Dr. Jones and asked if he would review your book for ACCN. He agreed to this (I believe he was happy to be asked) and he said he would add some personal notes as well. I am looking forward to reading the review. Dr. Jones is going to Europe for 6 weeks and so he said he needs until the end of May to complete the review.

I have also contacted Nola Haddadian, the ACCN Editor, to tell her than Dr. Jones will review the book.

We plan to put a small note in Infochem, the local newsletter for chemists and engineers, giving the Queen's alumni address as a way to order the book. I have heard others mention how much they have enjoyed reading your book.

Jean Cooley Jean Cooley

Syncrude
Edmonton Research Center
9421 - 17 Avenue
Edmonton, AB
T6N 1H4
(403) 970-6800

Fax No. (403) 970-6805

[illegible]

To: Dr Alfred Bader
Company: Alfred Bader Fine Arts
Phone: 414-277-0730
Fax: 414-277-0709

From: Roger Cowles
Company:
Phone: (403) 970-6953
Fax: (403) 970-6805
17/01/95
Date:
Pages including this cover page: 1

Comments: Thank you for your Fax of January 4; I have confirmed the facilities for the talks that you suggested. I have also spoken to Gerry Tertzakian and Norman Jones so that we can schedule the rest of your visit. Dr. and Mrs. Jones are already quite excited about your visit!

Could you please let me know your approximate arrival time on the Sunday because Gerry would like to entertain you and Mrs. Bader that evening. Of course, if you are arriving too late for that we can schedule it on Monday or Tuesday. I would also like a brief synopsis of each of the talks so that we can prepare material to publicize your visit.

Best wishes
Roger Cowles

August 21, 1996

Dr. Alfred Bader
Suite 622, 924 East Juneau Avenue
Milwaukee, Wisconsin, USA
53202

Dear Dr. Bader

Congratulations on achieving honorary FCIC! I was delighted to hear that the Chemical Institute of Canada has recognized your contributions to chemistry and particularly your contributions to the CIC. I know that the Edmonton region appreciated that you and Mrs. Bader could visit us and we could hear five of your talks. I also know that you have spoken at many national meetings. In addition I am certain that those people who have won the award you sponsor realize how special you are. Congratulations and thank you for all your contributions, especially your CIC contributions.

Dr. and Mrs. Jones came to Syncrude the other day. They both look great - Mrs. Jones appears to have recovered well from her operation. We toured them through our labs and they were interested in everything. I especially showed Dr. Jones some of the spectroscopic things we are doing. He has told me that he has asked his son to take them to Fort McMurray so they can see our plant. He has finished his review of your book. I think the review looks good. He has tried to include points which other reviewers did not cover. Also he has included some personal bits so it is very interesting to read.

I hope you and Mrs. Bader are enjoying the summer.

Sincerely

Jean

Jean Cooley

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

July 29, 1996

Dr. Jean Cooley
Research Associate
Syncrude Canada Ltd.
Edmonton Research Center
9421 - 17th Avenue
Edmonton, Alberta T6N 1H4
Canada

Dear Dr. Cooley:

I am sorry that a long trip to Europe has delayed my thanking you for your thoughtful letter of June 1st.

My autobiography is available in Canada, both from Queen's and from Little, Brown in Toronto. In Britain,it is sold by Weidenfeld & Nicolson at £14.99 and in the United States by Trafalgar Square at $25.00.

I very much look forward to seeing Norman Jones' review.

With all good wishes, I remain,

Yours sincerely,

AB/cw

June 1, 1996

Dr. Alfred Bader
Suite 622, 924 East Juneau Avenue
Milwaukee, Wisconsin, USA
53202

Dear Dr. Bader

I have attached a page from our local newsletter for CIC members (April edition). I had a small notice put in to tell members how to get your book - some members had mentioned that they were having difficulties. I got the information about Queen's from the Editor of Canadian Chemical News. I expect more people will want to read the book after Dr. Jones' review.

I have been away lately and unfortunately for me I missed the 3rd CIC Conference Lecturer. This year we invited Dr. Alf Rudin - a polymer chemist. I understand he presented two very good lectures. People in Edmonton are still talking about your visit and lectures. You were an inspiration to all of us.

I hope you and Mrs. Bader are enjoying the summer.

Sincerely

Jean Cooley

Jean Cooley

The ACPA will be holding this year's annual general meeting in Calgary at the Shell Canada Conference Room on June 15 at 1:00 P.M. Nominations are requested for Executive and Board positions: these should be received by Murray Fetzko by April 30, 1996. For further information, please contact him at (403) 472-6766.

[Thanks to Arthur Bollo-Kamara (Alberta Environmental Protection), ACPA President, for providing an outline of some of this information].

Science Fair Winners

The Edmonton Regional Science Fair is over for 1996. All the participants were certainly winners, but a few can be singled out for special attention.

The CIC Edmonton Section Award was won by Alia Hamdon-O'Brien, Grade 7, Parkview School in Edmonton for her project "Manipulating Synthesis of Zeolite". Honourable Mention went to Devon Bergh, Grade 5, Westlock School in Westlock for "The Truth About The Water You Drink".

The CIC National Award went to Jonathan Clark, Grade 7, Riverview School in Devon for "Reducing Polystyrene Waste". Honourable Mention went to Parmar Inderpal and Kris Campbell, Grade 9, Steele Heights School in Edmonton for "Charging to the Limits".

The Alex Taylor Memorial Senior Chemistry Award went to Kathryn Andrusky, Grade 12, Tofield School in Tofield for "Investigating Para-Aminobenzoic Acid".

Each of the three chemistry award winners also won first place in their Science Fair categories, plus several other special awards as well. Jonathan Clark's project was one of only five chosen to represent Edmonton at the Canada Wide Science Fair in North Bay / East Parry Sound, Ontario on May 11-19. Congratulations to all!

[Thanks to Martin Badke for this information].

Alfred Bader's Book

Many of you attended one or more of the lectures presented by last year's 75th CIC Conference Lecturer, Dr. Alfred Bader, and were charmed by his personality and impressed by his scholarship in chemistry, religion and the art of the Old Masters.

The subjects of most of these lectures are now available in a new book: *Adventures of a Chemist Collector*, by Alfred Bader, published by Weidenfeld & Nicholson, 288 pages (1995) Clothbound, ISBN 0-297-83461-4, US$29.95 (Canadian price not given).

In Canada, it might be simpler to purchase a copy through Dr. Bader's *alma mater*, Queen's University, by contacting:

Dawn-Marie Desjardins
Dept. of Alumni Affairs, Summer Hill
Queen's University
Kingston, Ontario K7L 3N6
Tel: 1-800-267-7837

[Thanks to Jean Cooley (Syncrude Canada Ltd.) for tracking down all this information].

Monnex Insurance

As a member of the CIC, you are in a select group in more ways than you might think. Along with members of APEGGA (the Association of Professional Engineers, Geologists & Geophysicists of Alberta), the Alberta Medical Association and a number of other organizations of professionals, you are eligible for home and automobile insurance coverage through Monnex Insurance Brokers Ltd. It is rumoured that they are able to offer us better deals because we professionals are lower risks (at least in the actuarial sense) than the bulk of the population.

You may find that the difference in rates between Monnex and your old insurer will help to pay for your CIC dues next year. Monnex in Edmonton is at 429-1112 (or 1-800-268-8955): just tell them that the CIC sent you.

REVIEWS

RCMP Lab Tour

A Review by Stan J. Backs

"When a man commits a crime, he always leaves something at the scene that was not there before, and carries away something that was not on him when he arrived."

Edmund Locard, Father of Forensic Trace Evidence Analysis (1901)

Trace evidence analysis is a major activity at the RCMP Forensic Laboratory in Edmonton. This evidence

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

June 19, 1996

Dr. Jean Cooley
Research Associate
Syncrude Canada Ltd.
Edmonton Research Center
9421 - 17th Avenue
Edmonton, Alberta T6N 1H4
Canada

Dear Dr. Cooley:

Thank you for your letter of June 1st to Dr. Bader.

He is in England through the end of July and will reply personally upon his return to Milwaukee.

Best wishes,

Cheryl

Cheryl Weiss
Office Manager

Too complicated

Rpue 5/9

Michael —
FYI Barry

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

January 24, 1997

Professor K. Barry Sharpless
Department of Chemistry
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, CA 92037

Dear Barry:

I was delighted to learn that you won the Roger Adams Award in Organic Chemistry. It couldn't happen to a greater guy.

I'm very puzzled not to have heard a word from Seth Harrison. I keep leaving messages at his office and had hoped to be able to arrange to get together with him while I am in New York from January 28 to 31.

Fond regards to you and Jan, as always,

AB/nik

organic compounds, and is best recognized for applying mass spectrometry to solve the structures of complex, nonvolatile polar natural products. His lab was one of the first to interface the use of chromatography with mass spectrometry to determine structures of compounds not previously tractable, such as complex peptides.

Rinehart is a coinventor of the mutasynthesis method of preparing new antibiotics—a technique in which the producing organism is mutated so that it cannot produce one subunit of the antibiotic, and then related subunits are added to produce new antibiotics.

In addition, Rinehart discovered didemnins, including didemnin B, in the sea squirt. Didemnin B is the first marine natural product to undergo clinical trials as an anticancer agent. So far, it mainly shows promise for treating non-Hodgkins lymphoma, a tumor prevalent in people with AIDS. He was also the first to isolate ecteinascidins, including ecteinascidin 743, from another sea squirt, which is now being tested as an antitumor agent in clinical trials in four countries. Rinehart's group helped publicize marine natural products as potential medicinal agents in television programs and in articles in the lay press.

After receiving a B.S. in chemistry from Yale University in 1950, Rinehart earned a Ph.D. degree in chemistry from the University of California, Berkeley, in 1954. He has published more than 373 research articles and holds more than 30 patents, including patents on didemnins and ecteinascidins. He was honored with a Research Achievement Award by the American Society of Pharmacognosy in 1989 and was named a Senior University Scholar at the University of Illinois, also in 1989.

ACS Award for Computers in Chemical & Pharmaceutical Research

Sponsored by IBM North America, Scientific & Technical Systems & Solutions

"For the past 50 years," **HAROLD A. SCHERAGA** has made "seminal use of computers to advance our knowledge in chemical science," notes a colleague. "He has profoundly affected the way chemists and biochemists use computers to study macromolecular chemistry." His main area of application has been macromolecules—determining how interatomic interactions lead to the thermodynamically stable structures of polypeptides and fibrous and globular proteins.

Scheraga, Todd Professor of Chemistry Emeritus at Cornell University, was among the first to employ computers to solve equations describing the orientation of asymmetrical molecules in solution under the influence of an external hydrodynamic field and subject to Brownian motion. These computations enabled double refraction of flow and non-Newtonian viscosity to be used to determine the size and shape of dissolved asymmetrical molecules.

Scheraga then used computers to evaluate the partition function and thermodynamic properties of liquid water, liquid D_2O, and aqueous hydrocarbon solutions for subsequent treatment of hydrophobic interactions. "This work opened up a whole field of investigations in this important area," points out a colleague. For example, Scheraga was able to suggest, and then explain, the importance of hydrophobic interactions for the helix-coil transition.

In addition, Scheraga was a pioneer in conformational energy calculations on polypeptides, proteins, and other biological molecules. His procedures are now used widely, including research in biotechnology and drug design. "His rigorous computational studies of proteins, nucleic acids, and other complex macromolecules have forged important theoretical and experimental links between diverse areas of physical chemistry, and led to numerous advances in our understanding of biopolymers," explains a colleague.

"He shows no sign of slowing down," adds another colleague. "Indeed, some of his recent work on new methods to solve the multiple minima problem is particularly novel, and defines the state of the art on this important problem."

Scheraga earned a B.S. degree in chemistry in 1941 at City College of New York and a Ph.D. degree in chemistry in 1946 at Duke University. He joined the Cornell University chemistry faculty in 1947 and was department chairman from 1960 to 1967. He has served on many advisory and editorial boards and international scientific commissions. His numerous honors include election to the National Academy of Sciences in 1966 and the Stein & Moore Award of the Protein Society in 1995. He has won American Chemical Society awards in biochemistry, colloid or surface chemistry, polymer chemistry, and the chemistry of biological processes. He also has won the William H. Nichols Medal of the ACS New York Section and the Linus Pauling Award of the Oregon, Portland, and Puget Sound Sections. He has authored two books and 975 journal articles.

Roger Adams Award in Organic Chemistry

Sponsored by Organic Reactions Inc. and Organic Syntheses Inc.

To appreciate the chemical passions of **K. BARRY SHARPLESS,** W. M. Keck Professor of Chemistry at Scripps Research Institute, La Jolla, Calif., one must go back to his childhood. He grew up in Philadelphia. But the lasting memory of his youth was the New Jersey shore, where his family spent many summers, weekends, and holidays. By the time he was eight years old, Sharpless, using a dinghy, was exploring the Manasquan River, which joins the Atlantic Ocean. By age 10, he was adept at catching crabs and eels. At age 14, he started working as the first mate on a charter boat.

"I grew up loving the sea and loving fishing in particular," he wrote after he received the Tetrahedron Prize for Creativity in Organic Chemistry in 1993 [*Tetrahedron,* **50,** 4235 (1994)]. "But unlike most fishermen I cared less for the size or quantity of the catch than for its rarity."

He was always hoping to catch something new. And he still does, except now his fishing ground is the periodic table and the catch he seeks is a practical reaction catalyzed by any of his favorite elements—selenium, titanium, and osmium

Sharpless grew up in a home that believed in Quaker values and he attended a Quaker school. "The Quakers encourage modesty, thrift, initiative, and enterprise," he wrote. "But the greatest good is being . . . useful."

Unlike many of his peers whose chemical careers span many areas, Sharpless has had a singular passion for the oxidation of olefins, especially by metal-catalyzed approaches. His peers characterize the reactions he has fished out of the periodic table as general, simple, and useful. The reactions have provided the pharmaceutical industry with inexpensive methods for making enantiomerically pure compounds.

One of his best known catches is asymmetric epoxidation of allylic alcohols [*J. Am. Chem. Soc.,* **102,** 5974 (1980)]. Because of its great scope, simplicity of operation, and reliability, this reaction, catalyzed by titanium and tartrate, is widely used by synthetic chemists.

Another key Sharpless reaction is asymmetric dihydroxylation, catalyzed by osmium and quinine [*J. Am. Chem. Soc.,* **110,** 1968 (1988)]. According to a col-

ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

July 31, 1996

Professor Barry Sharpless
Department of Chemistry
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, CA 92037

Dear Barry:

Enclosed please find copies of Jim Horns' invoice and Treatment Report for the restoration of your portrait. The painting was shipped both ways via Fed-Ex at a cost of $18.25 each way. Hence, your total cost is $536.50.

With best wishes from house to house,

AB/cw

Enclosures

By Appointment Only
ASTOR HOTEL SUITE 622
924 EAST JUNEAU AVENUE
MILWAUKEE WISCONSIN USA 53202
TEL 414 277-0730 FAX 414 277-0709

Pergamon

Tetrahedron Vol. 50, No. 15, pp. 4235-4258, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $6.00+0.00

0040-4020(94)E0067-4

Coelacanths and Catalysis*

K. Barry Sharpless

Department of Chemistry, The Scripps Research Institute
10666 North Torrey Pines Road, La Jolla, CA 92037

File

In 1938, THREE YEARS BEFORE I WAS BORN, a live coelacanth was taken from the waters off the eastern coast of South Africa. Previously known only in the fossil record from some hundred million years ago, the coelacanth and the implications of its discovery remained big news for years, fueling an enthusiasm for "creatures" that persisted for decades. Those of us born in the Forties grew up on photos of eminent scientists setting off on expeditions, their sun-burnt faces dwarfed by mountain explorer's garb, or making thumbs-up signs as they entered the water in scuba gear. We shared their confident expectation that the Loch Ness Monster, Sasquatch, the Yeti — even a dinosaur — soon would be taken alive.

I grew up loving the sea and loving fishing in particular, but unlike most fishermen I cared less for the size or quantity of the catch than for its rarity. Nothing could be more exciting than pulling (if not this time, then surely the next!) a mysterious and hitherto unknown creature from the water. Clearly, I wanted to catch my own coelacanth.

Reports of fishing expeditions usually are scorned by scientific journals. However, Sir Derek Barton, Chairman of the Executive Board of Editors of Tetrahedron Publications, must take some responsibility for the nature of this article since he suggested it might be a rather personal review of my chemistry, including some of the background leading up to it: first of all, my background is awash with fish and fishing, specifically in the Manasquan River and that part of the Jersey Shore where the Manasquan meets the Atlantic Ocean; and secondly, I do chemistry the way I used to fish.

---

*Dedicated to four MIT colleagues: to Dan Kemp, who showed me how one should teach and taught me never to confuse opportunism with good science; to fellow fishermen Glenn Berchtold and George Büchi, who from the very first, starting with their generous mentoring when I was a novice faculty member, set an example that was and always has been worth emulating; and to Satoru Masamune, my all-time chalk-talk companion of choice.

As to the chemistry, upon looking through the contributions from Tetrahedron Prize recipients who preceded me at this honorable writing task, I realize they organized their chemical careers in terms of the different areas and the discrete projects in those areas on which they have worked. Essentially all my chemical investigations, however, are in only one area, and I tend to view my activity there not in terms of projects, but in terms of two passions I have had since graduate school and where those passions led me:

> I am passionate about the Periodic Table, and selenium, titanium and osmium became my favorite elements;
>
> I am passionate about catalysis, and, having laid a hand on two splendid examples of this elusive phenomenon, nothing else ever will be as stimulating.

What the ocean was to me as a child, the Periodic Table is to the chemist; new reactivity is, of course, my coelacanth.

Even though I grew up in Philadelphia, if someone asks me where I'm from I usually say "the Jersey Shore," because that's where my family spent summers, as well as many weekends and holidays, with my father joining us whenever he could. My father had a flourishing one-man general surgery practice which meant he was perpetually on call. With him at home so little and practically guaranteed to be called away when he was, my mother liked being near family and friends at the Shore, where her parents had settled and established a fishery after emigrating from Norway. When I was a baby, my parents bought a lot on a bluff overlooking the Manasquan River about four miles up from where the river enters the Atlantic.

Like many scientists I was a very shy child, happier and more confident when on my own. My interest was totally absorbed by the river. In those days the incoming tide transformed our part of the river from a channel flanked by broad mud flats to a quarter-mile basin that exploded with life of myriad variety — about a dozen kinds of fish big enough to make it to the dinner table, plus blue crab, eel, and a bounty of fry and fingerlings that would graduate downstream to the ocean. I was obsessed with finding and observing everything that lived in the river and knowing everyone who worked on it.

My most delicious childhood memory is the excitement I experienced the very moment I awoke on almost every summer morning; the sound I associate with that feeling is the distant whine of my first scientific mentor's outboard motor. That was my wake-up call, and within minutes I was at the river's edge, waiting in the pre-dawn stillness for Elmer Havens and his father Ollie to make their way across the river from Herbertsville to pick me up to "help" them seine for crabs. Amused by my regularly walking along the bank to watch them haul their seine, Elmer eventually installed me in the boat, which he used for transportation as well as for steadying himself as he dragged the seine's deep-water end. Ollie walked one end of the seine along the shore, alarming the crabs gathered at the river's edge, and frightening them toward deeper water and so into the net's pocket. Chest deep in water and mud, Elmer walked parallel to his father, one arm clasping the seine, the other hooked over the boat's gunwale. Elmer and I, our heads close together, would speculate about the catch, taking into account all the variables — the weather, the season, the tide. Every hundred yards or so, Elmer doubled ahead toward the shore to draw the purse. I liked it best if a big eel or a snapping turtle got caught up in the net, making the water boil and the net flop into the air. I always hoped we'd catch something new.

I had a little dinghy, and my realm of exploration expanded in direct proportion to my rowing ability. The same tide that created this abundant estuary also was my nemesis, forever stranding me upriver in the narrows or perhaps at Chapman's Boat Yard, a mile down river and on the opposite bank. Since my parents couldn't keep me off the water, they opted for increasing the likelihood of my getting home unaided by giving me a little boat with an outboard. It wasn't long before I went down river all the way to the inlet (absolutely forbidden, of course), and, soon after, the prospect of new creatures to pull from the water lured me out through the rock jetties and into the ocean: at the time I was only seven or perhaps eight years old.

By the time I was ten, I ran crab and eel traps and supplied everyone we knew with fish as well; at fourteen I started working during the summer as the first (and only) mate on a charter boat. My parents allowed me to start mating when I was so young and small even for my age because I was offered a job on a relative's boat — little did my parents or I know that Uncle Dink, a cousin actually, offered me the job so he wouldn't have to pay a "full-sized" helper. I so wanted to keep working on the boats that it was years before I dared tell my parents what went on aboard the *Teepee*, like how the Coast Guard refused assistance to Dink because his boat was in chronic disrepair. (Consequently, some of our adventures at sea were memorable indeed — grappling hooks and guns have their place in the canon — and I mention this trove of Uncle Dink stories because for years my MIT colleagues begged me to tell them over and over again.)

On a charter boat the captain pilots the ship and finds the fish the customers reel in. Meanwhile the mate is over the boat like a dervish, skillfully arraying the water with fishly temptations — adjusting outriggers, finding the perfect combination of lure or bait and tackle, always mindful of the action on nearby boats competing for the same fish.* Since my friends were all mates we naturally agreed that enticing fish to bite was the greatest challenge, but I alone felt that getting the strike was the most fun, even more exciting than landing the fish. I worked as a mate almost daily every summer, right up until the day before I set out from New Jersey headed toward the biggest ocean and graduate school at Stanford University.

That was in 1963. In the spring of that year my inspiring Dartmouth College chemistry professor and first research director, Tom Spencer, talked me into delaying entering medical school to try a year of graduate school. He sent me to Stanford specifically to work for E. E. van Tamelen, Tom's own mentor at Wisconsin. The appeal of fishing was such that Tom, to my later regret, never succeeded in getting me to spend any summers working in his lab. In fact even in graduate school I expressed my ambivalence by continuing to fantasize about finding a boat out of Manasquan to skipper and by failing — this did not please v.T. — to do the simple paperwork required to renew my NSF predoctoral fellowship.

However, toward the end of my first year at Stanford a serendipitous misunderstanding catalyzed the complete transfer of my passion (some would say my monomania) from one great science to another, from fishing to chemistry. Before leaving for a lengthy European visiting professorship, v.T. sent me to the library to look for reactive inorganic species that might produce interesting transformations of organic compounds. My first projects with v.T. were selective oxidation of polyolefins and titanium-mediated deoxygenative coupling of alcohols, and I was already primed to appreciate useful chemistry employing "strange" elements after selecting the Wittig Reaction from a list of suggested topics for my student seminar. The Wittig Reaction really engaged my enthusiasm, and I ingenuously concluded that finding new reactions other chemists could use looked like a lot of fun.

---

*This diversion into fishing-as-metaphor-for-research could go on for pages: consider how when a boat was hooking tuna — the catch of choice — word spread by radio and the competition converged from every compass point. The hot boat's captain greeted this acknowledgment of his success with some anxiety: while he liked setting the other captains' agendas and pleasurably speculating that the parties on the other boats were considering chartering him next time, the secrets of his success nonetheless required protection, so trolling speeds were lowered to sink the lures and prevent rubberneckers from identifying them, and red herrings (literally, on occasion!) were casually displayed on the fish box.

Isaak Walton and John Hersey devoted whole books to this metaphor, so indulge me for a few more sentences. The handy process *vs.* product dichotomy that applies so neatly to much of human endeavor illuminates this fisherman-chemist comparison, too. Conventional wisdom places fly-fishing at the "process" end of the scale, while a "product" fisherman uses sonar to find a school before he bothers to get his line wet. Process person though I am, only the Manasquan River ran through my fishing days: trolling for the unknown always had more appeal than hooking a trout I already knew was there.

In any event upon v.T.'s return I discovered he had not intended for me to spend *all* those months immersed in the literature. While I had no research results to report, I did have a notebook filled with ideas and an eagerness to drop my line throughout the vastness of the Periodic Table. I don't think I've gone fishing in the literal sense a dozen times since then!

From van Tamelen, a Gilbert Stork protégé, I inherited enthusiastic disdain for "safe" problems,* deep admiration for traditional multistep organic synthesis and awe before selective biological catalysis: studying the squalene oxide/lanosterol cyclase enzyme left me impressed by enzymic selectivity but depressed by the difficulty of using enzymes for synthetic transformations. After getting a double dose of him in the classroom, Derek Barton became my model. At Dartmouth Tom Spencer taught a course on conformational analysis based on one he took at Wisconsin from William S. Johnson (Tom's uncle, in fact), then I experienced the original at Stanford.[†] Being wet behind the ears I took conformational analysis for granted: it was Sir Derek's search for new reactivity that electrified me. A postdoc with Jim Collman (the only person, I concede, who gets more excited about chemistry than I do) ignited my interest in using simple metal complexes to develop catalysts (in the Collman lab, incidentally, I had the privilege of many hours at the blackboard with labmate Bob Grubbs). Then before taking up my job at MIT, a postdoc with Konrad Bloch confirmed my hunch that impatience rendered me incompetent around enzymes. Konrad graciously let me start working on my own ideas when his proved much too frustrating for me.

One other part of my background seems to have contributed to my chemistry. The first American Sharpless ("Sharples" then) came to Pennsylvania in the Seventeenth Century not long after William Penn. My father was a practicing Quaker only as a child, but the values in our home were Quaker values, and I was educated in a Quaker school. The Quakers encourage modesty, thrift, initiative and enterprise, but the greatest good is being a responsible member of the community — being useful. "Elegant" and "clever" were the chemical accolades of choice when I started doing research, just as "novel" is high praise now. Perhaps the Quakers are responsible for me valuing "useful" most.

So that, with apologies to Sir Derek for taking such advantage of his suggestion, is my background as a chemist. I've been accused of going too far when I speculate that chirality fascinates me because I handled my umbilical cord *in utero*, but I'm quite sincere in proposing that the extraordinary training I received as a young chemist transformed an existing passion for discovering the unknown into the search for new reactivity, and that Quaker utilitarianism made the selective oxidation of olefins so appealing.

With respect to chemical reactions, "useful" implies wide scope, simplicity to run, and an essential transformation of readily available starting materials. Clearly, if useful new reactivity is the goal, investigating the transformations chemists rely on is the obvious strategy. The processes for the selective oxidation of olefins have long been among the most useful tools for day-to-day organic synthesis because of these appealing characteristics of olefins:

they are among the cheapest functionalized organic starting materials,
they can be carried "hidden" through conventional acid/base-catalyzed transformations, then "revealed" at will by adding heteroatoms through selective oxidations,
most simple olefins are prochiral, providing a prominent portal to the chiral world.

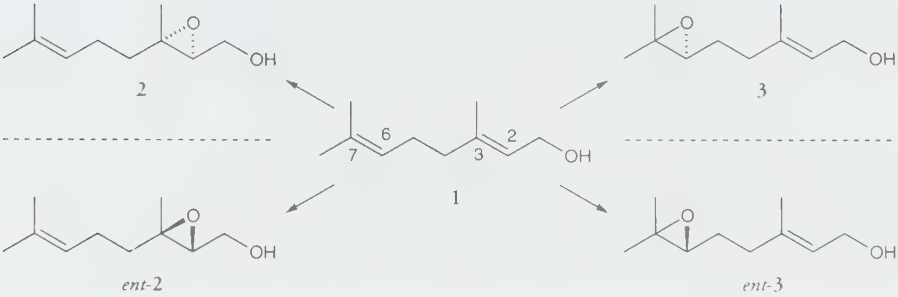
---

*Sat Masamune and Peter Dervan, fellow van Tamelen alumni, and I often discuss this shared legacy.

[†] When teaching MIT undergraduates I always said, "The lights came on with conformational analysis," without thinking where I picked up the phrase, but now I know: the previous Tetrahedron Prize article states, "Just as chemists of the Robinson generation worked without concern for stereochemical factors so we, in the early days, were working in ignorance of conformational considerations until Derek Barton showed us the light in 1950." The author is, of course, Bill Johnson.[1]

SCHEME I

Regio- and Enantioselective Monoepoxidations of Geraniol



The trisubstituted olefin geraniol, in addition to being one of my favorite smells, provides an excellent case study both for laying out the challenges of selective olefin oxidation as well as for noting some benchmarks in meeting those challenges.

As shown in scheme 1, geraniol has two trisubstituted olefinic units, one of which has a hydroxyl in the allylic position. Four monoepoxides are possible: making either racemic **2** or racemic **3** requires regio- (or chemo-) selectivity, while making each of the individual enantiomers requires enantioselectivity. When Henbest showed that the electronic deactivation by the oxygen substituent at C-1 causes peracids to prefer the 6,7-double bond (especially on the ester derivatives), making racemic **3** became possible.[2] When I started doing research in the Sixties, neither racemic **2** nor any of the enantiomers could be synthesized directly. Solving the other half of the regioselectivity problem was an obvious challenge, but enantioselectivity was considered well-nigh impossible.

In 1973 Bob Michaelson cracked the other half of the regioselectivity problem presented by geraniol.[3] Since early-transition-metal-catalyzed epoxidations with alkyl hydroperoxides proved highly selective for the 2,3-position, racemic **2** could be prepared as well.

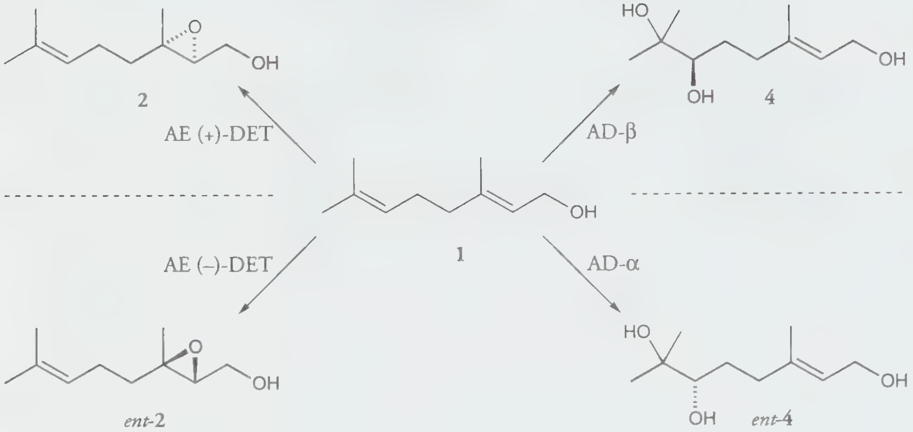
In 1980 Tsutomu Katsuki discovered the titanium-catalyzed asymmetric epoxidation (AE); the enantioselective oxidation of olefins bearing allylic hydroxyl groups made it possible to make either **2** or *ent*-**2** thus solving one side of the enantioselectivity problem.[4]

TABLE I

Some Widely-Used Catalytic Asymmetric Processes

Reported	Process
1968	Hydrogenation of functionalized olefins[7a,8a]
1978	Isomerization of allylic amines [8b,c,d]
1980	Titanium-catalyzed epoxidation of allylic alcohols [4,9a]
1988	Osmium-catalyzed dihydroxylation of isolated olefins [24,9b]
1990	Manganese-catalyzed epoxidation of isolated olefins [6,10]

SCHEME 2



The osmium-catalyzed asymmetric dihydroxylation (AD), discovered in 1987, subsequently was improved to the point that either **3** or *ent*-**3** could be made by way of the diol, an indirect solution to enantioselective epoxidation at the 6,7-position (scheme 2).[5]

In 1990 came the breakthrough introduction of enantioselectivity into existing salen ligand catalysts.[6] Eric Jacobsen's exciting manganese catalyst for isolated-olefin epoxidation came first and is still the leader, but the Jacobsen Epoxidation works best on only one of the six olefin-substitution classes. Nonetheless, its very existence is tantalizing, encouraging the hope that a general, off-the-shelf solution exists for the direct asymmetric epoxidation of the full range of isolated olefin substitution patterns.

The greater generality of man-made catalysts such as these compared with enzymes was noted first by Knowles[7a,c] and Kagan.[7b] During the lean times in the first decade of my career, their pioneering development of man's first highly enantioselective catalysts (the L-dopa synthesis that came out of Knowles' Monsanto lab was the asymmetric hydrogenation's first commercial application) sustained my faith that a catalyst for asymmetric oxidation could be found. Jack Halpern's mechanistic studies[7d] on asymmetric hydrogenation catalysis likewise inspired me. Several Japanese chemists, chief among them Ryoji Noyori,[7e] hugely extended both the scope and application of the asymmetric hydrogenation process.

This focused search has frustrated but never bored me even after so many years, and the geraniol paradigm illustrates why. My own investigations into the oxidation of olefins commenced at MIT in 1970, but, fittingly, I was back at Stanford on January 18, 1980, for Tsutomu Katsuki's dramatic discovery of the titanium-catalyzed asymmetric epoxidation.[4] Two years later the most scientifically stimulating and professionally gratifying collaboration of my career, the total syntheses of the eight L-hexoses with my MIT colleague Sat Masamune, capped the AE's discovery.[11] Previous articles[12] in a vein similar to this one describe that chemistry; understanding the AE's significance and putting that understanding to work are the purview here.

After the euphoria of completing the hexose syntheses, three years were spent developing, refining and finding more applications for the AE. During this time I returned to the search for new reactivity, but it was clear that my random, scattershot attempts were going nowhere,* so I was grateful for the opportunity to spend the first three months of 1987 as a Sherman Fairchild Scholar at Caltech.

Many universities and institutions have handsome Fairchild buildings, but Caltech, ever the bastion of collegiality and camaraderie, used its Fairchild grant to endow a program that brings scientists from many fields to be housed graciously in the sunshine for as long as a year. Since my research group's investigation of the AE had reached the point of diminishing returns, I left for Pasadena hoping to renew my mission.

I love reading journals, and I love mountains, so the Caltech library with its panoramic view of Mt. Wilson became my thinking place of choice. Every day Mt. Wilson offered new vistas, especially on those occasions when snow fell during the night. One morning the mountain was completely cloaked (the first time a freezing temperature was recorded in downtown LA, I recall), and the melting snow receded at such a clip I was sure I saw it happening. Mt. Wilson was the perfect backdrop for bringing my own big picture back into focus, and I returned to MIT eager to renew my search for new reactivity. Meditating on the AE yielded this lesson to guide that search:

> ligand-accelerated catalysis (the significance of which is documented in M. G. Finn's fine MIT thesis on the mechanism of the AE[13]), is crucial to the AE and not merely a feature of it; despite its rarity this phenomenon might be the agent for uncovering more catalytic processes

Of course the first and best-known example of ligand acceleration is found in Criegee's papers from the Thirties.[14] He observed that pyridine accelerates the reaction in his classic study of osmium tetroxide

---

*I have enormous admiration for colleagues who can keep multiple research projects alive and large groups humming, but the "monomania" that prevents me from being able to do that is my long suit as well, making it possible to concentrate — for years, actually — on a single topic. I know some chemists call my approach "intuitive," a term I've always thought underestimates the rigor that frames my method; perhaps "unstructured" or "contemplative" is more accurate. Many of my cohorts are quick and facile and can jump on a few interesting bits of data and start building tentative edifices that get taken apart and reassembled to suit new data. I, on the other hand, am ruminative: my training after all consisted of busily poking and perturbing the Manasquan River, a curriculum both urgent and leisurely, one that permitted exploration without assumptions and without the structure imposed by deadlines or competition or by knowing too little or too much. Since I was compelled by shyness to learn to do much on my own, there was (and is) no right or wrong way, only many ways, some more or less suited to a given endeavor. The discipline, nonetheless, is exacting: everything that can be observed should be observed, even if it is only recalled as the bland background from which the intriguing bits pop out like Venus in the evening sky. The goal is always finding something new, hopefully unimagined and, better still, hitherto unimaginable. When I became a bench- and desk-bound explorer the method stayed the same. I try to imagine away the packaging information arrives in, then let bits and pieces move around lazily, rather like objects tumbling slowly in zero gravity, but eventually, over time, exploring every possible relationship with other information that's previously arrived. Since joining the faculty of The Scripps Research Institute, I've discovered that ocean swimming and running on the beach provide an excellent medium for this kind of activity; however, in any climate the best catalyst is generous, stimulating conversation. This slow but endlessly fascinating method is like an exotic ritual courtship, full of displays of bright feathers or offerings of shiny metal or towers of sticks — what does it all, what does any of it mean? Enormous concentration is required to remember it all in a way that causes little sparks when certain conjunctions appear, making a connection with something noted previously, perhaps decades ago. Sadly, as I grow older, the connections become harder to summon up, so the sparks, though seeming as bright as ever, are less frequent. I describe this process at length because it's not the way most scientists approach their work, nor is it well suited to the demands of funding agencies that are railroaded into answering questions posed for political rather than scientific reasons, nor to the needs of graduate students who require publications to compete for jobs. Academic chemistry is much harder now, and I'm glad I was born when I was.

and olefins. Ironically, the lesson from the AE was directing me back toward Criegee, whose discoveries in olefin oxidation and osmylation were, in large measure, the jumping off point for my own research career.

I first looked into Criegee's process shortly after becoming an assistant professor at MIT. My attraction to the reaction of OsO_4 with olefins was inevitable. Osmium tetroxide not only accomplishes an important synthetic transformation, but it does so with a scope and reliability unique among reactions used for organic synthesis. It reacts *only* with olefins and it reacts with *all* olefins (slight poetic license here). Even R. B. Woodward valued Criegee's stoichiometric transformation so much he was willing to use 100 g of OsO_4 in one shot. Osmium's expense wasn't compatible with "useful," however and, since the existing catalytic variants were not very effective, I starting searching for a reliable catalytic method. In 1975 Kagayasu Akashi found a good process for us based on a hydroperoxide as oxidant, *tertiary*-butyl hydroperoxide (TBHP),[15] but the brass ring was ultimately captured that same year with the publication of the famous Upjohn process based on *N*-methyl morpholine-*N*-oxide (NMO).[16]

Throughout the rest of the Seventies osmium remained our primary tool for looking for new reactivity: we discovered that imido osmium(VIII) species effected stoichiometric *cis*-oxyamination of olefins in direct analogy to the *cis*-dihydroxylation of olefins by osmium tetroxide; even more effective catalytic versions of those transformations came shortly thereafter.

In 1977 I left MIT, where I had been a contented member of a wonderful chemistry faculty since 1970, for Stanford University, where I previously spent six contented years as a graduate student and postdoc, surrounded by a wonderful chemistry faculty. I never made the transition back to contentment at Stanford, probably because my research wasn't churning up much. This frustrated me and scared off potential graduate students who wanted publications, not a fishing expedition. In addition, at Stanford I remained awed by a faculty I worshiped when a graduate student, and I lacked the confidence to stand firm on issues, particularly faculty appointments, that meant a lot to me. In 1979 at about the same time I made the decision to return to MIT, Steve Hentges, who worked in our well-developed osmium imido area and already had the material for a good Ph.D. thesis in hand, decided to take on one more project before writing up.

The notion of an asymmetric ligand for osmium tetroxide had been knocking around the lab for years, and Steve first approached the idea by making several pyridines with chiral substituents at the 2-position; these gave diols with essentially 0% ee![17] Pyridine is only a modest ligand for osmium tetroxide, and we discovered any ortho substituent is lethal to binding. But since William Griffith at Imperial College showed that quinuclidine binds more strongly to OsO_4, I suggested trying the cinchona alkaloids, essentially substituted quinuclidines.[18] (Many chemists have expressed surprise at how quickly we arrived at what is now and may always be the best ligand framework for the AD: anyone with a natural products background and who is also a fan of Hans Wynberg's chemistry recognizes the cinchona alkaloids as the obvious next step.) The results were spectacular, even without taking into account a measurement error (discovered years later) that caused most of the ee's to be underreported by 5 to 15%![17]

Steve had a dramatic story to cap his thesis work, so he started writing; my attention was taken up by the decision to return to MIT: then a couple of months later Katsuki discovered an asymmetric process with ingredients so cheap it made working with osmium look like Rolls-Royce chemistry. Although the AE was only weakly catalytic in the early days,[19] its uniformly high ee's and nontoxic, inexpensive reagents were enough to completely divert our attention from its promising but stoichiometric predecessor, the OsO_4/cinchona asymmetric dihydroxylation.

The preceding paragraph has no doubt failed to deflect your attention from the obvious question: why didn't I try the Hentges ligands in the Upjohn system in 1979? Indeed, why did I propose the experiment in my NIH grant renewal in January, 1984, but not follow up on it? "As for the ligand," I wrote in

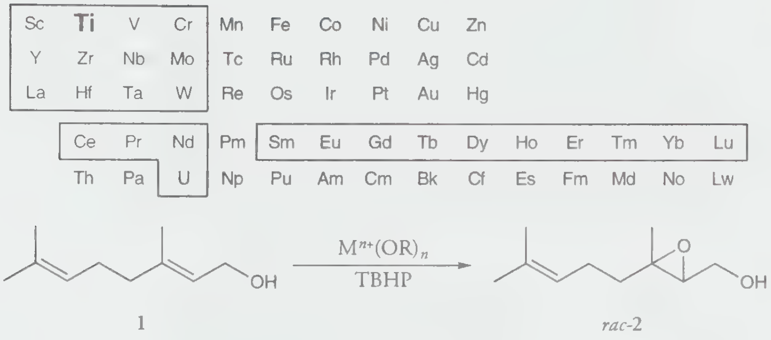


FIGURE I

Metals Catalyzing the Epoxidation of Allylic Alcohols by TBHP

Adding tartrate ligand *always* affects reactivity: the titanium system is accelerated; all twenty-four others are killed or dramatically slowed!

the proposal, "it is probably best to stay with the cinchona derivatives because the quinuclidine moiety is the best ligand we know of for Os(VIII) complexes. The substrate will be stilbene…the osmium catalyst will be recycled using an amine *N*-oxide. Ideally, both the osmium and the chiral alkaloid could be used in catalytic quantities. A successful system of this type could be of great practical importance."

Instead of poking and perturbing, the Jersey Shore School of Thinking's cardinal rule, I stuck with the odds logic suggested: ligands accelerate the reaction of OsO_4 with olefins, *but* they also bind avidly to the resulting osmate ester, lethally effecting catalyst turnover. This ability of ligands such as pyridine and quinuclidine to kill turnover in catalytic osmylation systems had been often observed in my laboratory. What I did not nor could not anticipate is the perfect balance cinchona alkaloids achieve in ligating ability, binding well enough to accelerate the key step, but weakly enough to slip off allowing the hydrolysis/reoxidation steps of the catalytic cycle to proceed. At the time, however, the precedents seemed clear, so the AD languished until 1987.

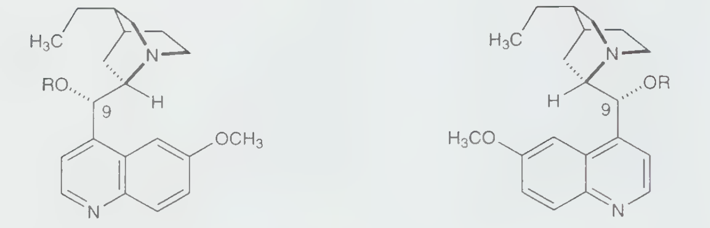
Unraveling the mechanism of the AE was largely the work of M. G. Finn.[13] His persistent exploration during the early- to mid-eighties of the AE's titanium-tartrate catalyst system exposed a complex mixture of species in dynamic equilibrium with one other.[20] M. G. discovered the main species $[Ti(DIPT)(O\text{-}i\text{-}Pr)_2]_2$ is substantially more active than the many other species present (significantly, it is five to ten times more active than $Ti(OR)_4$, a catalyst for the formation of racemic epoxy alcohol) and this rate advantage funnels catalysis through the appropriate tartrate-bearing species.

If the tartrate-induced acceleration of the titanium-catalyzed epoxidation reaction came as a surprise, investigating that phenomenon brought even more surprising results. We ultimately found twenty-four metals other than Ti that catalyze the epoxidation of allylic alcohols by TBHP (figure 1), but all these systems were strongly inhibited or killed by adding tartrate![21] Ligand-*de*celerated catalysis was clearly the rule while ligand *ac*celeration was the extraordinarily valuable exception.*

Shortly before I left for Caltech, Chris Burns, encouraged by Pui Tong Ho, presciently lobbied to resurrect the OsO_4/cinchona asymmetric dihydroxylation, and, without any encouragement from me I must admit, he embarked on the synthesis of a stoichiometric C_3-symmetric ligand for the AD.[22] A few

---

*For a detailed account of ligand-decelerated catalysis, see the discussion of the "tridentate fiasco" in reference 12a.



dihydroquinidine derivatives

dihydroquinine derivatives

FIGURE 2

Cinchona Alkaloid Ligands for the Asymmetric Dihydroxylation (AD)

months later, I, too, was recommitted to osmium, and when Bill Mungall and Georg Schröder reviewed the work from 1979 they uncovered ee's even better than previously reported. Meanwhile Eric Jacobsen attacked the problem from the mechanistic side, discovering that the ligand-dependent rate accelerations could be enormous.[23]

With these very encouraging results on the stoichiometric reaction just in, Istvan Markó joined the project. I was travelling at the time, and on his own initiative, unaware of the NIH proposal, he combined Hentges' system[17] with the reliable Upjohn NMO-based catalytic osmylation system,[16] immediately getting results indicating the reaction was catalytic.[24] However, unlike the dramatic "Eureka!" that accompanied the discovery of the AE, cautious optimism was the response to the catalytic AD and its initially modest ee's. Now, however, after six years of research since Markó's first experiments in October of 1987, the AD's utility rivals and often surpasses the AE's.[9]

Unlike the AE, for which Katsuki's initial tartrate ester ligands have yet to be eclipsed, the ligands for the AD have evolved substantially in effectiveness and scope through substitution at the C-9 hydroxyl.

The simple ester derivatives (*e.g.* the acetate and *para*-chlorobenzoate esters) gave way in 1990 and 1991 to aryl ether derivatives, first proposed by Yun Gao during a late night group meeting to address the mechanistic question of a possible ligating role of the ester carbonyl. Brent Blackburn made the phenyl ether which, to our surprise, gave good ee's, but was too hard to make to be competitive (at least with the two aromatic olefins tried) with the then dominant *para*-chlorobenzoate (CLB) ligand.

Almost a year later Declan Gilheany correctly predicted that aryl ethers should be better for aliphatic olefins than the CLB ligand,[25] and these results laid the foundation for a steady expansion of this ligand class, culminating in the phenanthryl ether ligand.[26] Another big jump in effectiveness came with the dimeric alkaloid ligands having a phthalazine core, first made by Jens Hartung in 1990.[27] Along with the pyrimidine ligands[28] whose development they inspired, they remain the best general ligands for the AD reaction.

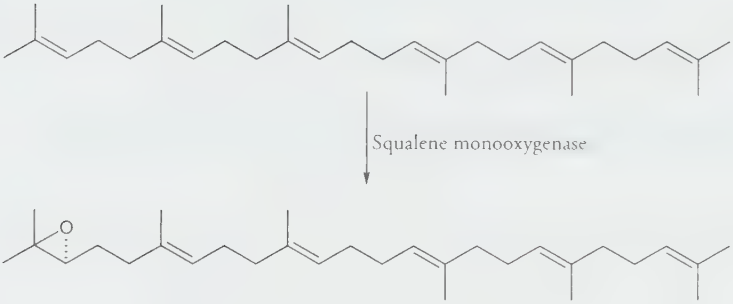
The search for better ligands has been paralleled by advances in catalyst turnover efficiency:

John Wai found both the second-catalytic-cycle problem and its partial remedy, slow addition of the olefin;[29]

Since ferricyanide in *tert*-butanol/water provides an excellent two-phase system for catalytic osmylation,[30] Hoi-Lun Kwong applied it to the AD solving the second-cycle problem and the need for slow addition;[31]

Willi Amberg found that adding organic sulfonamides greatly facilitates the rate of catalyst turnover for olefins whose osmate esters resist hydrolysis.[27]

SCHEME 3



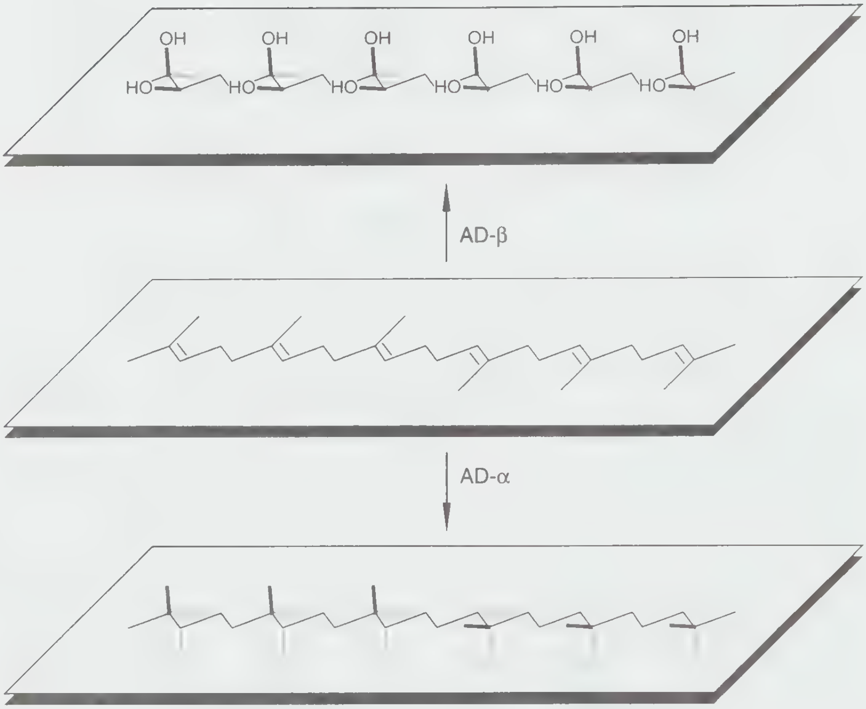
As the practicality (it has been scaled up to run in 4000 liter reactors with no ill effects on yield or ee[32]) and scope of the AD process grew, so did the pressure to understand the origin of its enantioselectivity. Mechanistic studies dating from the early Seventies by Alan Teranishi and Jan Bäckvall[33] were rekindled by Eric Jacobsen in 1987 and are now our major preoccupation. Some of the most important findings of the past three years will appear soon.[34]

While a complete and general solution to the geraniol paradigm's final challenge is tantalizingly within reach, comparing selectivity at the bench with selectivity in living systems remains striking. For example, the squalene monooxygenase in our livers unerringly deposits a single oxygen atom on the squalene molecule and, in so doing, further chooses only the *si*-enantioface of the terminal double bond (scheme 3).[35] On the other hand, the attempted AD of a single double bond of squalene does give the terminal diol in 96% ee. The preference for the terminal double bond is slight, however, and internal diols as well as tetraols also can be isolated from the reaction.[36] Thus while the AD catalyst cannot match the exquisite selectivity of the enzymic system, this very inability to discriminate between the six trisubstituted double bonds of squalene allows the exhaustive AD of squalene (scheme 4) in an overall yield of 79.8% for the AD-β reaction.[37]

Serial multistep reactions such as these are stymied by Bob Ireland's "arithmetic demon" — the geometric fall in yield in sequential chemical reactions. The AD of each double bond is one step in a procession of six dihydroxylations, each with a chemical and an optical yield, twelve yields in all. Thus the average yield of each step is $(0.798)^{1/12}$ or 98%, translating to 98% for each chemical yield, 96% ee for the single enantioselective reaction and 96% de for each of the five diastereoselective reactions. The high yield of a single enantiomer from the multiple hydroxylation events required to completely oxidize squalene reflects the reliability and selectivity of the AD process. Joel Hawkins' Berkeley lab kinetically resolved the chiral fullerene C_{76} resulting in the first enantiomerically pure allotrope of carbon, the AD's most intriguing use to date.[38]

My decision nearly twenty-five years ago to study the selective oxidation of olefins produced an unexpected bonus, one that gave me an opportunity to investigate uncharted territory on a scale that is more associated with the previous half-century than with our own. Selenium, titanium and osmium, my three most successful olefin oxidation catalysts, all had phobias associated with them that stunted their investigation. Selenium and osmium were considered highly toxic, and the peroxide oxidants used with titanium had a nasty reputation. Rarely did I find myself in another chemist's territory; likewise, few wanted to cast a line in mine.

SCHEME 4



Tracking these elements offers a rather curious way to view my research. Figure 3a plots the time course of their dominance (as measured by publications for want of a more qualitative ruler) during the past twenty-three years. Selenium came first, flourished, then ended abruptly. Osmium research came next, co-existing with selenium until both were eclipsed by titanium, the descendant of molybdenum and vanadium. Osmium made a strong comeback, knocking off titanium.

Figure 3b, charting my research with respect to catalytic transformations, looks quite unlike figure 3a, but relates directly to it. As my involvement with catalysis grew, the largely stoichiometric selenium reagents lost their appeal; titanium fell because the effectiveness of the titanium catalyst for the AE is modest, with about only twenty turnovers per titanium center before all activity is lost. Osmium, despite a bimodal presentation, was never actually out of the picture, merely quiescent until the discovery of the highly catalytic AD (it has been run to completion with as little as ¹⁄₅₀,₀₀₀ of osmium catalyst).

In figure 3b the only real defection from the steady growth of catalysis to dominion in my research was the 1982 trough caused by the hexose synthesis collaboration with Sat Masamune. Stepping out of the realm of catalysis is almost unimaginable to me now, nor is osmium ever likely to be dislodged. Naturally I hope it will be joined by new catalysts.

Ultimately, catalysis and its power are the engine driving my research. With nature's catalysts for inspiration, it was possible to imagine small, asymmetric catalysts. Achieving that revealed the previously unimaginable: highly enantioselective catalysis without "lock and key" binding; small catalysts tolerating a wide range of substrates, thus with a high likelihood for synthetic utility; the notion of ligand-accelerated

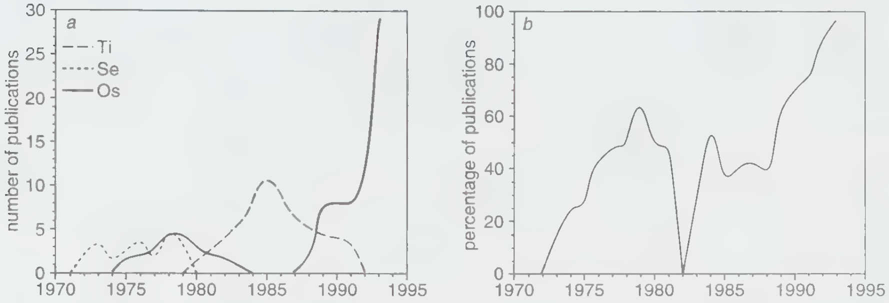


FIGURE 3

(a) Selenium, titanium and osmium chemistry; note the osmium line's bimodality.
(b) Growth of catalysis in my laboratory.

catalysis. The latter, I feel strongly, is the single most interesting finding to arise from the catalytic asymmetric epoxidation and dihydroxylation processes. Despite so far uncovering just these two ligand-accelerated systems and having identified a mere handful of others from the literature,[39] my research will continue to plumb the vastness of the Periodic Table for more examples: their potential for great utility overcomes my misgivings about their scarceness. I am, after all, the optimistic product of the generation that caught the coelacanth.

ACKNOWLEDGEMENT

Above all I thank and express my deep gratitude to my past and present coworkers at MIT, Stanford and The Scripps Research Institute. Many of you learned to tolerate my style of directing research (an oxymoron perhaps?); indeed, some of you flourished. Others were not well served, and to you I sincerely apologize. I'm exceedingly proud of you MIT undergraduates who got your feet wet in my lab and are embarking now on your own academic careers: remember you got your opportunities because Tom Spencer gave me mine and I expect you to do the same. Mentioning Tom brings me back, as so many things do, to E. E. van Tamelen: the bright flashes of his career remain of the first magnitude and still inspire me. And finally, my scientific career would have been unthinkable without the constant support and counsel of my wife, best friend — and ghost writer — Jan.

I also thank the National Institutes of Health (GM-28384) and the National Science Foundation (CHE-9296055) for their continuous financial support over the past twenty years, and more recently the William M. Keck Foundation for helping to make possible my present tenure at The Scripps Research Institute in La Jolla.

REFERENCES AND NOTES

1. Johnson, W.S. *Tetrahedron* **1991,** *47*, xi-1.
2. Henbest, H.B.; Wilson, R.A.L. *J. Chem. Soc.* **1957,** 1958.
3. Sharpless, K.B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973,** *95*, 6136.
4. Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980,** *102*, 5974.

5. (a) David Xu synthesized **4** and *ent*-**4** in 1991 during his work on the AD mechanism, from which synthesis of **3** and *ent*-**3** was implicit; two other groups reported this reaction sequence: (b) Corey, E.J.; Noe, M.C.; Shieh, W.C. *Tetrahedron Lett.* **1993,** *34,* 5995-5998; (c) Vidari, G.; Dapiaggi, A; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993,** *34,* 6485-6488; (d) Vidari, G.; Giori, A.; Dapiaggi, A; Lanfranchi, G. *Tetrahedron Lett.* **1993,** *34,* 6925-6928. Gerry Crispino's juvenile hormone III synthesis demonstrates the same conversion: (e) Crispino, G.A.; Sharpless, K.B. *Synthesis* **1993,** *8,* 777.
6. (a) Zhang, W.; Loebach, J.L.; Wilson, S.R. Jacobsen, E.N. *J. Am. Chem. Soc.* **1990,** *112,* 2801; (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990,** *31,* 7345.
7. (a) Knowles, W.S.; Sabacky, M.J. *J. Chem. Soc.; Chem. Commun.* **1968,** 1445; (b) Dang, T.P.; Kagan, H.B. *J. Chem. Soc.; Chem. Commun.* **1971,** 481 (c) Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D.; Weinkauff, D.J. *J. Am. Chem. Soc.* **1975,** *97,* 2567-2568. (d) See his excellent review: Halpern, J. *Science* **1982,** *217,* 401. (e) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980,** *102,* 7932-7934.
8. (a) Takaya, H.; Ohta, T. "Asymmetric Hydrogenation" In *Catalytic Asymmetric Synthesis,* Ojima, I. Ed.;VCH Publishers: New York, 1993; pp. 1-39; (b) Kumobayashi,H.; Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1978,** *100,* 3949; (c) Akutagawa, S.; Tani, K. "Asymmetric Isomerization of Allylamines" In *Catalytic Asymmetric Synthesis;* Ojima, I. Ed.;VCH Publishers, Inc.: New York, 1993; pp. 41-61. A history and review of the development of the asymmetric hydrogen migration of allylamines can be found in: (d) Otsuka, S.; Tani, K. *Synthesis* **1991,** 665-680.
9. For review chapters on both the AE and AD written largely by Roy Johnson despite being coauthored by both of us, see: (a) Johnson, R.A.; Sharpless, K.B. "Catalytic Asymmetric Epoxidation of Allylic Alcohols" In *Catalytic Asymmetric Synthesis,* Ojima, I. Ed.; VCH Publishers: New York, 1993; pp. 101-158; (b) Johnson, R.A.; Sharpless, K.B. "Catalytic Asymmetric Dihydroxylation" In *Catalytic Asymmetric Synthesis,* Ojima, I. Ed.; VCH Publishers: New York, 1993; pp. 227-272.
10. Jacobsen, E.N. "Asymmetric Catalytic Epoxidation of Unfunctionalized Olefins" In *Catalytic Asymmetric Synthesis,* Ojima, I. Ed.; VCH Publishers: New York, 1993; pp. 159-202.
11. (a) Ko, S.Y.; Lee, A.W.M.; Masamune, S.; Reed, L.A.; Sharpless, K.B.; Walker, F.J. *Science* **1983,** *220,* 949; (b) Ko, S.Y.; Lee, A.W.M.; Masamune, S.; Reed, L.A.; Sharpless, K.B.; Walker, F.J. *Tetrahedron* **1990,** *46,* 245.
12. (a) Sharpless, K.B. *CHEMTECH* **1985,** 692; (b) Sharpless, K.B. *Chem. Brit.* **1986,** *22,* 1.
13. M.G. Finn's thesis work has appeared in two full papers: (a) Woodard, S.S.; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991,** *113,* 106;(b) Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991,** *113,* 113.
14. (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936,** *522,* 75; (b) Criegee, R. *Angew. Chem.* **1937,** *50,* 153; (c) Criegee, R. *Angew. Chem.* **1938,** *51,* 519; (d) Criegee, R.; Marchand, B.; Wannowias, H. *Justus Liebigs Ann. Chem.* **1942,** *550,* 99.
15. Sharpless, K.B.; Akashi, K. *J. Am. Chem. Soc.* **1976,** *98,* 1986.
16. van Rheenen, V.; Kelly, R.C.; Cha, P.Y. *Tetrahedron Lett.* **1976,** 1973.
17. Hentges, S.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980,** *102,* 4263.
18. (a) Cleare, M.J.; Hydes, P.C.; Griffith, W.P.; Wright, M.J. *J. Chem. Soc., Dalton Trans.* **1977,** 941; (b) Griffith, W.P.; Skapski, A.C.; Woode, K.A.; Wright, M.J. *Inorg. Chim. Acta* **1978,** *31,* L413.
19. Five years later Bob Hanson made the simple but wonderful discovery that adding molecular sieves to the reaction dramatically increases catalyst turnover so that the AE process became truly catalytic: Hanson, R.M.; Sharpless, K.B. *J. Org. Chem.* **1986,** *51,* 1922.

20. Steve Pedersen provided invaluable structural results to aid M.G. Finn's studies during this period. Steve's work gave us our first glimpse into the dynamic world of complex mixtures in rapid equilibrium with each other. His contributions are summarized in: Sharpless, K.B. *Chemica Scripta (Sweden)* **1987,** *27,* 521. These studies led to no new catalysts, but they drove home our appreciation for the absolute need for a ligand-acceleration effect in catalyst systems where ligand exchange is rapid.
21. Kirshenbaum, K.S. Ph.D. Thesis, Massachusetts Institute of Technology, 1985.
22. Burns, C.J. Ph.D. Thesis, Massachusetts Institute of Technology, 1989.
23. Jacobsen, E.N.; Markó, E.I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989,** *111,* 737.
24. Jacobsen, E.N.; Markó, E.I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988,** *110,* 1968.
25. Shibata, T.; Gilheany, D.G.; Blackburn, B.K.; Sharpless, K.B. *Tetrahedron Lett.* **1990,** *31,* 3817.
26. Sharpless, K.B.; Amberg, W.; Beller, M.; Chen, H,; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991,** *56,* 4585.
27. Sharpless, K.B.; Amberg, W.; Bennani, Y.; Crispino, G.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang, Z.M.; Xu, D.; Zhang, X.L. *J. Org. Chem.* **1992,** *57,* 2768.
28. Crispino, G.; Jeong, K.S.; Kolb, H.; Wang, Z.M.; Xu, D.; Sharpless, K.B. *J. Org. Chem.* **1993,** *58,* 1958.
29. Wai, J.S.M.; Markó, I.; Svendsen, J.S.; Finn, M.G.; Jacobsen E.N.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989,** *111,* 1123.
30. Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990,** *55,* 766.
31. Kwong, H.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K.B. *Tetrahedron Lett.* **1990,** *31,* 2999.
32. Private communication from Dr. Yun Gao of Sepracor, Inc., Marlborough, MA.
33. Sharpless, K.B.; Teranishi, A.Y.; Bäckvall, J.E. *J. Am. Chem. Soc.* **1977,** *99,* 3120.
34. (a) Jacobsen, E.N.; Markó, E.I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989,** *111,* 737; (b) Göbel, T.; Sharpless, K.B. *Angew. Chem., Int. Ed. Eng.* **1993,** *32,* 1329; (c)Norrby, P.O.; Kolb, H., Sharpless, K.B. *Organometallics,* in press; (d) Kolb, H.C.; Andersson, P.G.; Bennani, Y.L.; Crispino, G.A.; Jeong, K.S.; Kwong, H.L.; Sharpless, K.B. *J. Am. Chem. Soc.*, in press; (e) Kolb, H.C; Andersen, P.G.; Sharpless, K.B. *J. Am. Chem. Soc.* in press; (f) Kwong, H.L. Ph.D. Thesis, Massachusetts Institute of Technology, 1993.
35. (a) Boar, R.B.; Damps, K. *Tetrahedron Lett.* **1974,** 3731; (b) Barton, D.H.R.; Jarman, T.R.; Watson, K.G.; Widdowson, D.A.; Boar, R.B.; Damps, K. *J. Chem. Soc., Chem. Commun.* **1974,** 861; (c) Barton, D.H.R.; Jarman, T.R.; Watson, K.G.; Widdowson, D.A.; Boar, R.B.; Damps, K. *J. Chem. Soc., Perkin I* **1975,** 1134.
36. Crispino, G.; Sharpless, K.B. *Tetrahedron Lett.* **1992,** *33,* 4273.
37. Crispino, G.A.; Ho, P.T.; Sharpless, K.B. *Science* **1993,** *259,* 64.
38. Hawkins, J.M.; Meyer, A. *Science* **1993,** *260,* 1918-1920.
39. With the help of my former postdoctoral coworkers Carsten Bolm and David Berrisford, I commenced writing some years ago a review of the ligand-acceleration phenomenon in catalysis. The article remains unfinished, but one beautiful example of the ligand-acceleration effect developed by the catalysis group at Ciba-Geigy Central Research deserves mention. All the ligand effects in that system are strikingly similar to the AD's, and yet their process involves a *heterogeneous* catalyst. In a production scale process, Ciba-Geigy asymmetrically hydrogenates α-ketoesters to lactate esters over a platinum catalyst modified by — cinchona alkaloid ligands! (a) Orito, Y.; Imai, S.; Niwa, S,; Nguyen, G.-H. *J. Synth. Org. Chem. Jpn.* **1979,** *37,* 173; (b) Orito, Y.; Imai, S.; Niwa, S, *J. Synth.*

H.P. Jensen and K.B. Sharpless, An Improved Procedure for the Direct Oxidation of Olefins to α-Diketones by Potassium Permanganate in Acetic Anhydride, *J. Org. Chem.*, *39*, 2314 (1974).

H.P. Jensen and K.B. Sharpless, Selenium Dioxide Oxidation of *d*-Limonene—a Reinvestigation, *J. Org. Chem.*, *40*, 264 (1975).

K.B. Sharpless and M.W. Young, Olefin Synthesis. Rate Enhancement of the Elimination of Alkyl Aryl Selenoxides by Electron-Withdrawing Substituents, *J. Org. Chem.*, *40*, 947 (1975).

K.B. Sharpless, D.W. Patrick, L.K. Truesdale, and S.A. Biller, A New Reaction. Stereospecific Vicinal Oxyamination of Olefins by Alkyl Imido Osmium Compounds, *J. Am. Chem. Soc.*, *97*, 2305 (1975).

K.B. Sharpless, A.O. Chong, and J.A. Scott, Rapid Separation of Organic Mixtures by Formation of Metal Complexes, *J Org. Chem.*, *40*, 1252 (1975).

K.B. Sharpless and D.R. Williams, The Reactions of Olefins with Permanganate, Ruthenium Tetroxide, and Osmium Tetroxide; Dependence of Rate on Degree of Substitution, *Tetrahedron Lett.*, 3045 (1975).

J.A. Nelson, S. Kahn, T.A. Spencer, K.B. Sharpless, and R.B. Clayton, Some Aspects of Substrate Specificity in Biological Demethylation at C4 of Steroids, *Bioorgan. Chem.*, *4*, 363 (1975).

K.B. Sharpless, K.M. Gordon, R.F. Lauer, D.W. Patrick, S.P. Singer, and M.W. Young, The Utility of Selenium Reagents in Organic Synthesis, *Chemica Scripta* (Sweden), Vol. 8A, 9 (1975).

K.B. Sharpless and Kageyasu Akashi, Oxidation of Alcohols to Aldehydes by Reagents Derived from Chromyl Chloride, *J Am. Chem. Soc.*, *97*, 5927 (1975).

K.B. Sharpless, T. Hori, L.K. Truesdale, and C.O. Dietrich, Allylic Amination of Olefins and Acetylenes by Imido Selenium Compounds, *J. Am. Chem. Soc.*, *98*, 269 (1976).

K.B. Sharpless and K.M. Gordon, Selenium Dioxide Oxidation of Ketones and Aldehydes. Evidence for the Intermediacy of β-Ketoseleninic Acids, *J. Am. Chem. Soc.*, *98*, 300 (1976).

K.B. Sharpless and T. Hori, Allylic Amination of Olefins and Acetylenes by Imido Sulfur Compounds, *J. Org. Chem.*, *41*, 176 (1976).

K.B. Sharpless, A.O. Chong, and K. Oshima, Osmium Catalyzed Oxyamination of Olefins by Chloramine-T, *J. Org. Chem.*, *41*, 177 (1976).

K.B. Sharpless and K. Akashi, Osmium Catalyzed Vicinal Hydroxylation of Olefins by *tert*-Butyl Hydroperoxide Under Alkaline Conditions, *J. Am. Chem. Soc.*, *98*, 1986 (1976).

K.B. Sharpless, K. Akashi, and K. Oshima, Ruthenium Catalyzed Oxidation of Alcohols to Aldehydes and Ketones by Amine-*N*-Oxides, *Tetrahedron Lett.*, 22503 (1976).

K.B. Sharpless and S.P. Singer, 1,2-Diamination of 1,3-Dienes by Imido Selenium Compounds, *J. Org. Chem.*, *41*, 2504 (1976).

R.C. Michaelson, R.E. Palermo, and K.B. Sharpless, Chiral Hydroxamic Acids as Ligands in the Vanadium Catalyzed Asymmetric Epoxidation of Allylic Alcohols by *tert*-Butyl Hydroperoxide, *J. Am. Chem. Soc.*, *99*, 1990 (1977).

A.O. Chong and K.B. Sharpless, On the Mechanism of the Molybdenum and Vanadium Catalyzed Epoxidation of Olefins by Alkyl Hydroperoxides, *J. Org. Chem.*, *42*, 1587 (1977).

K.B. Sharpless, A.Y. Teranishi, and J.-E. Bäckvall, Chromyl Chloride Oxidations of Olefins. Possible Role of Organometallic Intermediates in the Oxidations of Olefins by Oxotransition Metal Species, *J. Am. Chem. Soc.*, *99*, 3120 (1977)

A.O. Chong, K. Oshima, and K.B. Sharpless, Synthesis of Dioxo(*tert*-alkylimido)Osmium(VIII) and Oxotris(*tert*-alkylimido)Osmium(VIII) Complexes. Stereospecific Vicinal Diamination of Olefins, *J. Am. Chem. Soc.*, *99*, 3420 (1977).

M.A. Umbreit and K.B. Sharpless, Allylic Oxidation of Olefins by Catalytic and Stoichiometric Selenium Dioxide with *tert*-Butyl Hydroperoxide, *J. Am. Chem. Soc.*, *99*, 5526 (1977).

J.-E. Bäckvall, M.W. Young, and K.B. Sharpless, Vicinal Acetoxychlorination of Olefins by Chromyl Chloride in Acetyl Chloride, *Tetrahedron Lett.*, 3523 (1977).

T. Hori, S.P. Singer, and K.B. Sharpless, Allylic Deuteration and Tritiation of Olefins with *N*-Sulfinylsulfonamides, *J. Org Chem.*, *43*, 1456 (1978).

S.P. Singer and K.B. Sharpless, Synthesis of *d,l*-Gabaculine Utilizing Direct Allylic Amination as the Key Step, *J. Org. Chem.*, *43*, 1448 (1978).

T. Hori and K.B. Sharpless, Synthetic Applications of Arylselenenic and of Arylseleninic Acids. Conversion of Olefins to Allylic Alcohols and to Epoxides, *J. Org. Chem.*, *43*, 1689 (1978).

K. Akashi, R.E. Palermo, and K.B. Sharpless, A Major Improvement in the Osmium Catalyzed Vicinal Hydroxylation of Olefins by *tert*-Butyl Hydroperoxide, *J. Org. Chem.*, *43*, 2063 (1978).

D.W. Patrick, L.K. Truesdale, S.A. Biller, and K.B. Sharpless, Stereospecific Vicinal Oxyamination of Olefins by Alkyl Imido Osmium Compounds, *J. Org. Chem.*, *43*, 2628 (1978).

T. Frejd and K.B. Sharpless, A New Rearrangement of *N*-Arylhydroxamic Acids Catalyzed by Seleninic Acids and Phenylselenenyl Chloride, *Tetrahedron Lett.*, 2239 (1978).

E. Herranz and K.B. Sharpless, Improvements in the Osmium Catalyzed Oxyamination of Olefins by Chloramine-T, *J. Org Chem.*, *43*, 2544 (1978).

E. Herranz and S.A. Biller, and K.B. Sharpless, Osmium-Catalyzed Vicinal Oxyamination of Olefins by *N*-Chloro-*N*-Argentocarbamates, *J. Am. Chem. Soc.*, *100*, 3596 (1978).

L.S. Liebeskind, K.B. Sharpless, R. D. Wilson, and J.A. Ibers, The First d^0 Metallooxaziridines. Amination of Olefins, *J. Am. Chem. Soc.*, *100*, 7061 (1978).

S. Current and K.B. Sharpless, Carbonyl Participation in the Addition of *p*-Chlorophenylselenenyl Bromide to (*E*)-4-Hexenal: A New Route to 2,6-Dideoxyglycosides, *Tetrahedron Lett.*, 5075 (1978)

J.-E. Bäckvall, K. Oshima, R.E. Palermo, and K.B. Sharpless, Some Reactions of *N*-(2-hydroxyalkyl)-*p*-toluenesulfonamides and *N*-allyl-*p*-toluenesulfonamides, *J. Org. Chem.*, *44*, 1953 (1979).

T. Hori and K.B. Sharpless, Conversion of Allylic Phenylselenides to the Rearranged Allylic Chlorides by *N*-Chlorosuccinimide. Mechanism of Selenium Catalyzed Allylic Chlorination of β–Pinene, *J. Org. Chem.*, *44*, 4208 (1979)

T. Hori and K.B. Sharpless, Selenium Catalyzed Non-Radical Chlorination of Olefins with *N*-Chlorosuccinimide, *J. Org. Chem.*, *44*, 4204 (1979).

B. Chabaud and K.B. Sharpless, Oxidation of Acetylenes with *tert*-Butyl Hydroperoxide Catalyzed by Selenium Dioxide α,α'-Dioxygenation of Internal Alkynes, *J. Org. Chem.*, *44*, 4202 (1979).

B.E. Rossiter, T.R. Verhoeven, and K.B. Sharpless, Stereoselective Epoxidation of Acyclic Allylic Alcohols. A Correction of Our Previous Work, *Tetrahedron Lett.*, 4733 (1979).

K.B. Sharpless and T.R. Verhoeven, Metal-Catalyzed, Highly Selective Oxygenations of Olefins and Acetylenes with *tert*-Butyl Hydroperoxide. Practical Considerations and Mechanisms, *Aldrichimica Acta*, *12*, 63 (1979).

M.A. Umbreit and K.B. Sharpless, Deoxygenation of Epoxides with Lower Valent Tungsten Halides: *trans*-Cyclododecene, *Org. Syn.th*, *60*, 29 (1981).

E. Herranz and K.B. Sharpless, Osmium-Catalyzed Vicinal Oxyamination of Olefins by *N*-Chloro-*N*-Metallocarbamates, *J Org. Chem.*, *45*, 2710 (1980).

S.G. Hentges and K.B. Sharpless, Asymmetric Induction in the Reaction of Osmium Tetroxide with Olefins, *J. Am. Chem Soc.*, *102*, 4263 (1980).

S.G. Hentges and K.B. Sharpless, Improved Procedure for the Oxyamination of Olefins with Trioxo(*tert*-butylimido)osmium(VIII), *J. Org. Chem.*, *45*, 2257 (1980).

T. Katsuki and K.B. Sharpless, The First Practical Method for Asymmetric Epoxidation, *J. Am. Chem. Soc.*, *102*, 5974 (1980).

E. Herranz and K.B. Sharpless, Osmium Catalyzed Vicinal Oxyamination of Olefins by Chloramine-T: *cis*-2-(*p*-Toluenesulfonamido)-cyclohexanol and 2-Methyl-3-(*p*-toluenesulfonamido)-2-pentanol, *Org. Synth.*, *61*, 85 (1983).

B.E. Rossiter, T. Katsuki, and K.B. Sharpless, Asymmetric Epoxidation Provides Shortest Routes to Four Chiral Epoxy Alcohols which are Key Intermediates in Syntheses of Methymycin, Erythromycin, Leukotriene C-1 and Disparlure, *J. Am Chem. Soc.*, *103*, 464 (1981).

D.J. Morgans, K.B. Sharpless, and S.G. Traynor, Epoxy Alcohol Rearrangements: Hydroxyl Mediated Delivery of Lewis Acid Promoters, *J. Am. Chem. Soc.*, *103*, 462 (1981).

E. Herranz and K.B. Sharpless, Osmium Catalyzed Vicinal Oxyamination of Olefins by *N*-Chloro-*N*-Argento-Carbamates: *threo-N*-(1-Hydroxy-1,2-Diphenyl-2-yl) Ethyl Carbamate, *Org. Synth.*, *61*, 93 (1981).

P.H.J. Carlsen, T. Katsuki, V.S. Martin, and K.B. Sharpless, A Greatly Improved Procedure for Ruthenium Tetroxide-Catalyzed Oxidations of Organic Compounds, *J. Org. Chem.*, *46*, 3936 (1981).

V.S. Martin, S.S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K.B. Sharpless, Kinetic Resolution of Racemic Allylic Alcohols by Enantioselective Epoxidation. A Route to Substances of Absolute Enantiomeric Purity?, *J. Am. Chem. Soc.*, *103*, 6237 (1981)

T. Katsuki, A.W.M. Lee, P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, D. Tuddenham, and F.J. Walker, Synthesis of Saccharides and Related Polyhydroxylated Natural Products 1: Simple Alditols, *J. Org. Chem.*, *47*, 1373 (1982).

P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, S.M. Viti, Synthesis of Saccharides and Related Polyhydroxylated Natural Products 2: Simple Deoxyalditols, *J. Org. Chem.*, *47*, 1378 (1982).

A.W.M. Lee, V.S. Martin, S. Masamune, K.B. Sharpless, and F.J. Walker, Synthesis of Saccharides and Related Polyhydroxylated Natural Products 3: Efficient Conversion of 2,3-*erythro*-Aldoses to 2,3-*threo*-Aldoses, *J. Am. Chem. Soc., 104*, 3515 (1982).

M.A. Warpehoski, B. Chabaud, and K.B. Sharpless, Selenium Dioxide Oxidation of Endocyclic Olefins. Evidence for a Dissociation-Recombination Pathway, *J. Org. Chem., 47*, 2897 (1982).

N.C. Gonnella, K. Nakanishi, V.S. Martin, and K.B. Sharpless, General Method for Determining Absolute Configurations of Acyclic Allylic Alcohols, *J. Am. Chem. Soc., 104*, 3775 (1982).

K.B. Sharpless, C.H. Behrens, T. Katsuki, A.W.M. Lee, V.S. Martin, M. Takatani, S.M. Viti, F.J. Walker, and S.S. Woodard, Stereo- and Regioselective Openings of Chiral 2,3-Epoxy Alcohols. Versatile Routes to Optically Pure Natural Products and Drugs. Unusual Kinetic Resolutions., *Pure and Applied Chemistry, 55*, 589 (1983).

L.A. Reed, Y. Ito, S. Masamune, and K.B. Sharpless, Synthesis of Saccharides and Related Polyhydroxylated Natural Products. 4. α-D-and β-D-C-Glycopyranosides (2,6-Dialkyl-Substituted Tetrahydropyrans), *J. Am. Chem. Soc.*, 104, 6468 (1982).

S.Y. Ko, A.W.M. Lee, S. Masamune, L.A. Reed, K.B. Sharpless, and F.J. Walker, Total Synthesis of the *L*-Hexoses, *Science, 220*, 949 (1983).

J.G. Hill, B.E. Rossiter, and K.B. Sharpless, Anhydrous *tert*-Butyl Hydroperoxide in Toluene. The Preferred Reagent for Applications Requiring Dry TBHP., *J. Org. Chem., 48*, 3607 (1983).

S. Miyano, L.D.L. Lu, S.M. Viti, and K.B. Sharpless, Kinetic Resolution of Racemic β-Hydroxyamines by Enantioselective *N*-Oxide Formation., *J. Org. Chem., 48*, 3608 (1983).

K.B. Sharpless, S.S. Woodard and M.G. Finn, On the Mechanism of Titanium-Tartrate Catalyzed Asymmetric Epoxidation, *Pure and Appl. Chem.*, 55, 1823 (1983).

C.H. Behrens and K.B. Sharpless, New Transformations of 2,3-Epoxy Alcohols and Related Derivatives. Easy Routes to Homochiral Substances, *Aldrichimica Acta, 16*, 4 (1983).

L.D.L. Lu, R.A. Johnson, M.G. Finn, and K.B. Sharpless, Two New Asymmetric Epoxidation Catalysts. Unusual Stoichiometry and Inverse Enantiofacial Selection, *J. Org. Chem., 49*, 728 (1984).

K.B. Sharpless, Discovery of the Titanium-Catalyzed Asymmetric Epoxidation—A Personal Account., *Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research XXVII Stereospecificity in Chemistry and Biochemistry*, November 7-9, 1983, Houston, Texas, 1984.

B.E. Rossiter and K.B. Sharpless, Asymmetric Epoxidation of Homoallylic Alcohols. Synthesis of (–)-γ-Amino-β-(*R*)-Hydroxybutyric Acid (GABOB). *J. Org. Chem., 49*, 3707 (1984).

J.M. Hawkins and K.B. Sharpless, *threo-N,N'*-Bis (α-methylbenzyl) sulfamide: A Readily Available Chiral Ligand for Asymmetric Lithium Aluminum Hydride Reductions. *J. Org. Chem., 49*, 3861, (1984).

I.D. Williams, S.F. Pedersen, K.B. Sharpless, and S.J. Lippard, Crystal Structures of Two Titanium Tartrate Asymmetric Epoxidation Catalysts, *J. Am. Chem. Soc., 106*, 6430 (1984).

J.G. Hill, K.B. Sharpless, C.M. Exon, and R. Regenye, Enantioselective Epoxidation of Allylic Alcohols: (*2S,3S*)-3-Propyloxiranemethanol, *Org. Synth., 63*, 66 (1984).

C.E. Adams, F.J. Walker, and K.B. Sharpless, Enantioselective Synthesis of Swainsonine, A Trihydroxylated Indolizidine Alkaloid, *J. Org. Chem., 50*, 420 (1985).

K.B. Sharpless, A New Strategy For Full Control of Relative Stereochemistry Expands the Role of Asymmetric Synthesis, *Chemica Scripta* (Sweden), *25*, 71 (1985).

M.G. Finn, and K.B. Sharpless, On the Mechanism of Asymmetric Epoxidation with Titanium-Tartrate Catalysts, "Asymmetric Synthesis," Vol. 5, James D. Morrison, Ed.; Academic Press, Inc., New York, (1985), Chapter 8, pp. 247-308.

J.M. Klunder, M. Caron, M. Uchiyama, and K.B. Sharpless, Chlorohydroxylation of Olefins with Peroxides and Titanium Tetrachloride, *J. Org. Chem., 50*, 912 (1985).

K.S. Kirshenbaum and K.B. Sharpless, Improved Procedure for the Tungstate-catalyzed Epoxidation of α,β-Unsaturated Acids, *J. Org. Chem., 50*, 1979 (1985).

M.J. Schweiter and K.B. Sharpless, The Asymmetric Epoxidation of *tert*-Butyl Substituted Allylic Alcohols, *Tetrahedron Lett.*, 2543 (1985).

M. Caron and K.B. Sharpless, Ti(O*i*Pr)$_4$-Mediated Nucleophilic Openings of 2,3-Epoxy Alcohols. A Mild Procedure for Regioselective Ring-Opening, *J. Org. Chem., 50*, 1557 (1985).

J.M. Chong and K.B. Sharpless, Nucleophilic Opening of 2,3-Epoxy Acids and Amides Mediated by Ti(O*i*Pr)$_4$. Reliable C-3 Selectivity, *J. Org. Chem., 50*, 1560 (1985).

S. Miyano, L.D.L. Lu, S.M. Viti and K.B. Sharpless, Kinetic Resolution of Racemic β–Hydroxyamines by Enantioselective *N*-Oxide Formation, *J. Org. Chem., 50*, 4350 (1985).

J.M. Chong and K.B. Sharpless, Regioselective Openings of 2,3-Epoxy Acids with Organocuprates, *Tetrahedron Lett.*, 4683 (1985).

C.H. Behrens, S.Y. Ko, F.J. Walker, and K.B. Sharpless, Selective Transformation of 2,3-Epoxy Alcohols and Related Derivatives. Strategies for Nucleophilic Attack at Carbon-1, *J. Org. Chem.*, *50*, 5687 (1985).

C.H. Behrens and K.B. Sharpless, Selective Transformations of 2,3-Epoxy Alcohols and Related Derivatives. Strategies for Nucleophilic Attack at Carbon-3 or Carbon-2, *J. Org. Chem.*, *50*, 5696 (1985).

T. Katsuki and K.B. Sharpless, Method for Asymmetric Epoxidation, U.S. Patent 4,471,130, 1984, assigned to Stanford University.

K.B. Sharpless, The Discovery of Titanium-Catalyzed Asymmetric Epoxidation, *CHEMTECH*, 692 (1985)

J.M. Hawkins, J.C. Dewan, and K.B. Sharpless, Dioxomolybdenum(VI)-Substituted 2,6-Pyridinedimethanol Complexes New Five-Coordinate Species, *Inorg. Chem.*, *25*, 1501 (1986).

K.B. Sharpless, The Discovery of the Asymmetric Epoxidation, *Chem. Brit.*, *22*, 1 (1986)

R.M. Hanson and K.B. Sharpless, Procedure for the Catalytic Asymmetric Epoxidation of Allylic Alcohols in the Presence of Molecular Sieves, *J. Org. Chem.*, *51*, 1922 (1986).

K.B. Sharpless and R.A. Johnson, Metal-Mediated Halohydrin Formation, U. S. Patent 4,560,811, 1985, assigned to the Massachusetts Institute of Technology.

J.M. Klunder, S.Y. Ko, and K.B. Sharpless, Asymmetric Epoxidation of Allyl Alcohol: Efficient Routes to Homochiral β-Adrenergic Blocking Agents, *J. Org. Chem.*, *51*, 3710 (1986).

K.S. Kirshenbaum and K.B. Sharpless, Regioselective Nucleophilic Opening of *erythro*- and *threo*-2,3 Epoxy Alcohols, *Chem Lett.*, 11 (1987).

Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H. Masamune, and K.B. Sharpless, Catalytic Asymmetric Epoxidation and Kinetic Resolution: Modified Procedures Including In Situ Derivatization, *J. Am. Chem. Soc.*, *109*, 5765 (1987)

S.Y. Ko and K.B. Sharpless, *In Situ* Opening of Epoxy Alcohols: A Convenient Alternative to the Isolation of Unstable Epoxy Alcohols, *J. Org. Chem.*, *51*, 5413 (1986).

K.B. Sharpless, Architecturally Interesting Metal Complexes with Thermodynamically Dictated Structures, *Chemica Scripta* (Sweden), *27*, 521 (1987).

S.Y. Ko, H. Masamune, and K.B. Sharpless, *p*-Nitrobenzoate Esters of Epoxy Alcohols: Convenient Synthons for Water-Soluble Epoxy Alcohols, *J. Org. Chem.* *52* , 667 (1987).

A.D. Elbein, T. Szumilo, B.A. Sanford, K.B. Sharpless, and C.E. Adams, Effect of Isomers of Swainsonine on Glycosidase Activity and Glycoprotein Processing, *Biochemistry*, *26*, 2502 (1987).

S.F. Pedersen, J.C. Dewan, R.R. Eckman, and K.B. Sharpless, Unexpected Diversity in the Coordination Chemistry of Tartrate Esters with Titanium(IV), *J. Am. Chem. Soc.*, *109*, 1279 (1987).

J.M. Klunder and K.B. Sharpless, A Convenient Synthesis of Sulfinate Esters from Sulfonyl Chlorides, *J. Org. Chem.*, *52*, 2598 (1987).

J.M. Hawkins and K.B. Sharpless, Asymmetric Epoxidation Models: An Alkyl Hydroperoxide Dependent Change in Mechanism, *Tetrahedron Lett.*, *28*, 2825 (1987).

E.N. Jacobsen, I. Markó, W.S. Mungall, G. Schröder, and K.B. Sharpless, Asymmetric Dihydroxylation *via* Ligand-Accelerated Catalysis, *J. Am. Chem. Soc.*, *110*, 1968 (1988).

K.B. Sharpless, Catalytic Asymmetric Epoxidation, *Janssen Chimica Acta*, *6*, 3 (1988).

P. Carlier, W.S. Mungall, G. Schröder, and K.B. Sharpless, Enhanced Kinetic Resolution and Enzyme-Like Shape Selectivity, *J. Am. Chem. Soc.*, *110*, 2978 (1988).

C. Bolm, W.M. Davis, R.L. Halterman, and K.B. Sharpless, Synthesis and Crystal Structure of a Chiral C_3-Symmetric Monophosphine, *Angew. Chem., Int. Ed. Engl.*, *27*, 835 (1988).

Y. Gao and K.B. Sharpless, $Ti(O\text{-}i\text{-}Pr)_4$-Mediated Formation of 2,3-Epithio Alcohols from 2,3-Epoxy Alcohols, *J. Org. Chem.*, *53*, 4114 (1988).

Y. Gao and K.B. Sharpless, Asymmetric Synthesis of Both Enantiomers of Tomoxetine and Fluoxetine. Selective Reduction of 2,3-Epoxycinnamyl Alcohol with Red-Al, *J. Org. Chem.*, *53*, 4081 (1988).

M. Caron, P.R. Carlier, and K.B. Sharpless, Regioselective Azide Opening of 2,3-Epoxy Alcohols by $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$: Synthesis of α-Amino Acids, *J. Org. Chem.*, *53*, 5185 (1988)

C. Bolm and K.B. Sharpless, Synthesis of a C_3-Symmetric Phospha[2.2.2] Cyclophane, *Tetrahedron Lett.*, *29*, 5101 (1988).

Y. Gao and K.B. Sharpless, Vicinal Diol Cyclic Sulfates: Like Epoxides Only More Reactive, *J. Am. Chem. Soc., 110,* 7538 (1988).

J.M. Klunder, T. Onami, and K.B. Sharpless, Arenesulfonate Derivatives of Homochiral Glycidol: Versatile Chiral Building Blocks for Organic Synthesis, *J. Org. Chem., 54,* 1295 (1989).

E.N. Jacobsen, I. Markó, M.B. France, J.S. Svendsen, and K.B. Sharpless, Kinetic Role of the Alkaloid Ligands in Asymmetric Catalytic Dihydroxylation, *J. Am. Chem. Soc., 111,* 737 (1989).

J.S.M. Wai, I. Markó, J.S. Svendsen, M.G. Finn, E.N. Jacobsen and K.B. Sharpless, A Mechanistic Insight Leads to a Greatly Improved Osmium-Catalyzed Asymmetric Dihydroxylation Process, *J. Am. Chem. Soc., 111,* 1123 (1989).

S.Y. Ko, A.W.M. Lee, S.A. Masamune, L.A. Reed, III, K.B. Sharpless, and F.J. Walker, Total Synthesis of the L-Hexoses, *Tetrahedron, 46,* 245 (1990).

W. Bartmann and K.B. Sharpless, eds., "Stereochemistry of Organic and Bioorganic Transformations," VCH Verlagsgesellschaft, Weinheim, 1987.

B.B. Lohray, Y. Gao and K.B. Sharpless, One Pot Synthesis of Homochiral Aziridines and Aminoalcohols from Homochiral 1,2-Cyclic Sulfates, *Tetrahedron Lett., 30,* 2623 (1989).

J.S. Svendsen, I. Markó, E.N. Jacobsen, Ch. P. Rao, S. Bott and K.B. Sharpless, On the Structure of Osmium Tetroxide-Cinchona Alkaloid Complexes, *J. Org. Chem., 54,* 2263 (1989).

B.B. Lohray, T.H. Kalantar, B.M. Kim, C.Y. Park, T. Shibita, J.S.M. Wai and K.B. Sharpless, Documenting the Scope of the Catalytic Asymmetric Dihydroxylation, *Tetrahedron Lett., 30,* 2041 (1989).

B.M. Kim and K.B. Sharpless, Cyclic Sulfates Containing Acid-Sensitive Groups and Chemoselective Hydrolysis of Sulfate Esters, *Tetrahedron Lett., 30,* 655, (1989).

C.J. Burns, C.A. Martin, and K.B. Sharpless, Tartrate-Like Ligands in the Asymmetric Epoxidation, *J. Org. Chem., 54,* 2826 (1989).

P.R. Carlier and K.B. Sharpless, Studies on the Mechanism of the Asymmetric Epoxidation: A Ligand Variation Approach, *J Org. Chem., 54,* 4016 (1989).

G.D.H. Dijkstra, R.M. Kellogg, and H. Wynberg; J.S. Svendsen, I. Markó and K.B. Sharpless, Conformational Study of Cinchona Alkaloids. A Combined NMR, Molecular Mechanics and X-Ray Approach, *J. Am. Chem. Soc., 111,* 8069 (1989).

K.B. Sharpless and I.E. Markó, Ligand-Accelerated Catalytic Asymmetric Dihydroxylation using Dihydroquinidine and Dihydroquinidine Esters as Ligands, U.S Patent 4,871,855, 1989 assigned to the Massachusetts Institute of Technology.

M. Hayashi, F. Okamura. T. Toba, N. Oguni. and K.B. Sharpless, Kinetic Resolution of Racemic β–Hydroxy Amines by Enantioselective N-Oxide Formation, *Chem. Lett., 547* (1990).

R.M. Pearlstein, B.K. Blackburn, W.M. Davis, and K.B. Sharpless, Structural Characterization of the Pseudoenantiomeric *Cis*-Dioxo Osmium(VI) Esters of Chiral Diols with Cinchona Alkaloid Ligands, *Angew. Chem., Int. Ed. Engl., 29,* 639, (1990).

H. Kwong, C. Sorato, Y. Ogino, H. Chen, and K.B. Sharpless, Preclusion of the "Second Cycle" in the Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins Leads to a Superior Process, *Tetrahedron Lett., 31,* 2999, (1990).

B. Moon Kim and K.B. Sharpless, Heterogeneous Catalytic Asymmetric Dihydroxylation: Use of a Polymer-Bound Alkaloid, *Tetrahedron Lett., 31,* 3003, (1990).

K.B. Sharpless, R. Hanson, and S.Y. Ko, Catalytic Asymmetric Epoxidation, U.S. Patent 4,900,847, 1990 assigned to the Massachusetts Institute of Technology.

T. Shibata, D.G. Gilheany, B.K. Blackburn, and K.B. Sharpless, Ligand-Based Improvement of Enantioselectivity in the Catalytic Asymmetric Dihydroxylation of Dialkyl Substituted Olefins, *Tetrahedron Lett., 31,* 3817, (1990).

B. Moon Kim and K.B. Sharpless, A Short Route to β-Lactams: Use of Cyclic Sulfites From *Syn*-2,3-Dihydroxy Esters, *Tetrahedron Lett., 31,* 4317, (1990).

R.A. Johnson and K.B. Sharpless, Addition Reactions with Formation of Carbon-Oxygen Bonds: (ii) Asymmetric Methods of Epoxidation, "Comprehensive Organic Synthesis," Vol. 7, Barry M. Trost, Ed.; Pergamon Press, (1991), pp. 389-436.

S.S. Woodard, M.G. Finn, and K. Barry Sharpless, The Mechanism of Asymmetric Epoxidation. 1. Kinetics, *J. Am. Chem Soc., 113,* 106, (1991).

M.G. Finn and K.B. Sharpless, Mechanism of Asymmetric Epoxidation. 2. Catalyst Structure, *J. Am. Chem. Soc., 113,* 113, (1991).

P.R. Fleming and K.B. Sharpless, Selective Transformations of *threo*-2,3-Dihydroxy Esters., *J. Org. Chem., 56,* 2869, (1991).

R. Oi and K.B. Sharpless, Stereospecific Conversion of Chiral 1,2-Cyclic Sulfates to Chiral Imidazolines., *Tetrahedron Lett., 32,* 999, (1991).

C. Park, B. Moon Kim, and K.B. Sharpless, Catalytic Osmylation of Conjugated Dienes: A One-Pot Stereoselective Synthesis of Polyols., *Tetrahedron Lett.*, *32*, 1003, (1991).

B. McKee, D. Gilheany, and K.B. Sharpless, *R,R*-1,2-Diphenyl-1,2-ethanediol (stilbene diol)., *Org. Synth.*, *70*, 47, (1991).

K.B. Sharpless and I.E. Markó, Ligand-Accelerated Catalytic Asymmetric Dihydroxylation, U.S. Patent 4,965,364, 1990 assigned to Massachusetts Institute of Technology.

K.B. Sharpless, J.M. Klunder, and T. H. Onami, Optically Active Derivatives of Glycidol, U. S. Patent 4,946,974, 1990 assigned to Massachusetts Institute of Technology.

Y. Ogino, H. Chen, H.L. Kwong, and K.B. Sharpless, On the Timing of Hydrolysis/Reoxidation in the Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins Using Potassium Ferricyanide as the Reoxidant., *Tetrahedron Lett.*, *32*, 3965, (1991).

K.B. Sharpless, W. Amberg, M. Beller, H. Chen, J. Hartung, Y. Kawanami, D. Lübben, E. Manoury, Y. Ogino, T. Shibata, T. Ukita, New Ligands Double the Scope of the Catalytic Asymmetric Dihydroxylation of Olefins., *J. Org. Chem.*, *56*, 4585, (1991).

R. Oi and K.B. Sharpless, Facile Synthesis of Enantiopure *trans*-2,3-Diphenyl-1,4-Diazabicyclo[2.2.2.]Octane, *Tetrahedron Lett.*, *32*, 4853, (1991).

Y. Ogino, H. Chen, E. Manoury, T. Shibata, M. Beller, D. Lübben, and K.B. Sharpless, A Ligand Structure-Enantioselectivity Relationship for the Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins, *Tetrahedron Lett.*, *32*, 5761, (1991).

B. McKee, T. Kalantar, and K.B. Sharpless, Subtle Effects in the Asymmetric Epoxidation: Dependence of Kinetic Resolution Efficiency on the Monodentate Alkoxide Ligands of the Bystander Titanium Center, *J. Org. Chem.*, *56*, 6966 (1991)

R. Oi and K.B. Sharpless, Asymmetric Dihydroxylation of Acrolein Acetals: Synthesis of Stable Equivalents of Enantiopure Glyceraldehyde and Glycidaldehyde, *Tetrahedron Lett.*, *33*, 2095 (1992).

K.B. Sharpless, W. Amberg, Y. Bennani, G. Crispino, J. Hartung, K. Jeong, H. Kwong, K. Morikawa, Z.M. Wang, D. Xu, and X.L. Zhang, The Osmium-Catalyzed Asymmetric Dihydroxylation (AD): A New Ligand Class and a Process Improvement, *J. Org. Chem.*, *57*, 2768 (1992).

K.S. Jeong, P. Sjö, and K.B. Sharpless, Asymmetric Dihydroxylation of Enynes, *Tetrahedron Lett.*, *33*, 3833 (1992).

G. Crispino and K.B. Sharpless, Asymmetric Dihydroxylation of Squalene, *Tetrahedron Lett.*, *33*, 4273 (1992)

T. Kalantar and K.B. Sharpless, Transformations of Hydroxy Cyclic Sulfates: Stereospecific Conversion to 2,3,5-Trisubstituted Tetrahydrofurans, *Acta Chemica Scandinavica*, 47, 307 (1993).

L. Wang and K.B. Sharpless, Catalytic Asymmetric Dihydroxylation of Cis-Disubstituted Olefins, *J. Am. Chem. Soc.*, *114*, 7568 (1992).

D. Xu, G. A. Crispino, and K.B. Sharpless, Selective Asymmetric Dihydroxylation (AD) of Dienes, *J. Am. Chem. Soc.*, *114*, 7570 (1992).

T. Hashiyama, K. Morikawa, and K.B. Sharpless, α-Hydroxy Ketones in High Enantiomeric Purity from Asymmetric Dihydroxylation of Enol Ethers, *J. Org. Chem.*, *57*, 5067 (1992).

W. Amberg, Y.L. Bennani, R.J. Chadha, G.A. Crispino, W.D. Davis, J. Hartung, K.-S. Jeong, Y. Ogino, T. Shibata, and K.B. Sharpless, Syntheses and Crystal Structures of the Cinchona Alkaloid Derivatives used as Ligands in the Osmium-Catalyzed Asymmetric Dihydroxylation (AD) of Olefins, *J. Org. Chem.*, *58*, 844 (1993).

R.A. Johnson and K.B. Sharpless, Catalytic Asymmetric Epoxidation of Allylic Alcohols, "Catalytic Asymmetric Synthesis," Iwao Ojima, Ed.; VCH Publishers (1993).

R.A. Johnson and K.B. Sharpless, Catalytic Asymmetric Dihydroxylation, "Catalytic Asymmetric Synthesis," Iwao Ojima, Ed.; VCH Publishers (1993).

Z.M. Wang, X.L. Zhang, K.B. Sharpless, S.C. Sinha, A. Sinha-Bagchi, and E. Keinan, A General Approach to γ-Lactones via Osmium-Catalyzed Asymmetric Dihydroxylation. Synthesis of (–)- and (+)-Muricatacin, *Tetrahedron Lett.*, *33*, 6407 (1992).

E. Keinan, S.C. Sinha, A. Sinha-Bagchi, Z.M. Wang, X.L. Zhang, and K.B. Sharpless, Synthesis of All Four Isomers of Disparlure Using Osmium-Catalyzed Asymmetric Dihydroxylation, *Tetrahedron Lett.*, *33*, 6411 (1992).

H.C. Kolb and K.B. Sharpless, A Simplified Procedure for the Stereospecific Transformation of 1,2-Diols into Epoxides, *Tetrahedron*, *48*, 10515 (1992).

G.A. Crispino, P.T. Ho, and K.B. Sharpless, Selective Perhydroxylation of Squalene: Taming the Arithmetic Demon, *Science*, *259*, 64 (1993).

G.A. Crispino and K.B. Sharpless, Enantioselective Synthesis of Both Enantiomers of 7,7-Dimethyl-6,8-dioxabicyclo-[3.2.1]octane *via* Regioselective Asymmetric Dihydroxylation, *Synlett*, *1*, 47 (1993) .

H.C. Kolb, Y.L. Bennani, and K.B. Sharpless, Short and Practical Syntheses of (*R*)-(–)-Carnitine and (*R*)-(–)-γ-Amino-β-hydroxybutyric Acid (GABOB), *Tetrahedron: Asymmetry*, *4*, 133 (1993).

D. Xu and K.B. Sharpless, A Simple Route to Enantiomerically Enriched Oxazolidin-2-ones, *Tetrahedron Lett.*, *34*, 951 (1993).

Y.L. Bennani and K.B. Sharpless, Asymmetric Dihydroxylation (AD) of *N,N*-Dialkyl and *N*-Methoxy-*N*-methyl α,β-and β,γ-Unsaturated Amides, *Tetrahedron Lett.*, *34*, 2079 (1993).

Y.L. Bennani and K.B. Sharpless, Asymmetric Synthesis of γ-Hydroxy α,β-Unsaturated Amides via an AD-Elimination Process; Synthesis of (+)-Coriolic Acid, *Tetrahedron Lett.*, *34*, 2083 (1993).

Z.M. Wang, X.L. Zhang, and K.B. Sharpless, Asymmetric Dihydroxylation of Aryl Allyl Ethers, *Tetrahedron Lett.*, *34*, 2267 (1993).

S. Okamoto, K. Tani, F. Sato, K.B. Sharpless, and D. Zargarian, Synthesis of Optically Active Secondary Allylic Alcohols from Allylsilanes via Successive Asymmetric Dihydroxylation (AD) and Peterson Olefination Reactions, *Tetrahedron Lett.*, *34*, 2509 (1993).

G. Crispino, K.S. Jeong, H. Kolb, Z.M. Wang, D. Xu, and K.B. Sharpless, Improved Enantioselectivity in Asymmetric Dihydroxylations of Terminal Olefins Using Pyrimidine Ligands, *J. Org. Chem.*, *58*, 1958 (1993).

T. Göbel and K.B. Sharpless, Temperature Effects in Asymmetric Dihydroxylation: Evidence for a Stepwise Mechanism *Angew. Chem., Int. Ed. Engl.*, *32*, 1329 (1993).

P.G. Andersson and K.B. Sharpless, A Dramatic Ligand Effect on the Relative Reactivities of Substituted Alkenes with Osmium Tetroxide, *J. Am. Chem. Soc.*, *115*, 7047 (1993).

M.S. VanNieuwenhze and K.B. Sharpless, Kinetic Resolution of Racemic Olefins via Asymmetric Dihydroxylation, *J. Am Chem. Soc.*, *115*, 7864 (1993).

Z.M. Wang and K.B. Sharpless, Asymmetric Dihydroxylation of α-Substituted Styrene Derivatives, *Synlett*, *8*, 603 (1993).

P.J. Walsh and K.B. Sharpless, Asymmetric Dihydroxylation (AD) of α,β-Unsaturated Ketones, *Synlett*, *8*, 605 (1993)

G.A. Crispino and K.B. Sharpless, Enantioselective Synthesis of Juvenile Hormone III in Three Steps from Methyl Farnesoate, *Synthesis*, *8*, 777 (1993).

D.V. McGrath, G.D. Brabson, K.B. Sharpless, and L. Andrews, Reinvestigation of the Infrared Spectra of Oxoosmium (VI) Esters by Isotopic Labeling, *Inorganic Chemistry*, *32*, 4164 (1993).

P.J. Walsh, Y.L. Bennani, and K.B. Sharpless, Asymmetric Dihydroxylation (AD)/Cyclization of *N*-DiBoc Allylic and Homoallylic Amines: Selective Differentiation of the Hydroxyl Groups, *Tetrahedron Lett.*, *34*, 5545 (1993)

K. Morikawa, J. Park, P.G. Andersson, T. Hashiyama, and K.B. Sharpless, Catalytic Asymmetric Dihydroxylation of Tetrasubstituted Olefins, *J. Am. Chem. Soc.*, 115, 8463 (1993).

K. Morikawa and K.B. Sharpless, Double Diastereoselection in Asymmetric Dihydroxylation, *Tetrahedron Lett.*, *34*, 5575 (1993).

M. Arrington, Y.L. Bennani, T. Göbel, P. Walsh, S.-H. Zhao, and K.B. Sharpless, Modified Cinchona Alkaloid Ligands Improved Selectivities in the Osmium Tetroxide Catalyzed Asymmetric Dihydroxylation (AD) of Terminal Olefins, *Tetrahedron Lett.*, *34*, 7375 (1993).

R. Oi and K.B. Sharpless, 3-(1*S*,2-Dihydroxyethyl)-1,5-Dihydro-3*H*-2,4-Benzodioxepine, *Org. Synth.*, in press.

Z.-M. Wang and K.B. Sharpless, Asymmetric Dihydroxylation of Tertiary Allylic Alcohols, *Tetrahedron Lett.*, in press

Norrby, P-O, Kolb, H., and K.B. Sharpless, Calculations on the Reaction of Ruthenium Tetroxide with Olefins Using Density Functional Theory (DFT). Implications for the Possibility of Intermediates in the Osmium-catalyzed Asymmetric Dihydroxylation (AD), *Organometallics*, in press.

G. Crispino, A. Makita, Z.-M. Wang, and K.B. Sharpless, A Comparison of Ligands Proposed for the Asymmetric Dihydroxylation, *Tetrahedron Lett.*, in press.

H.C. Kolb, P.G. Andersson, Y.L. Bennani, G.A. Crispino, K.-S. Jeong, H.-L. Kwong, and K.B. Sharpless, On "The Origin of High Enantioselectivity in the Dihydroxylation of Olefins Using Osmium Tetroxide and Cinchona Alkaloid Catalysts", *J Am. Chem. Soc.*, in press.

I. Henderson, K.B. Sharpless, and C.-H. Wong, Synthesis of Carbohydrates via Tandem Use of the Osmium-Catalyzed Asymmetric Dihydroxylation and Enzyme-Catalyzed Aldol Addition Reactions, *J. Am. Chem. Soc.*, in press.

M.S. VanNieuwenhze and K.B. Sharpless, The Asymmetric Dihydroxylation of *cis*-Allylic Alcohols and Homoallylic Alcohols, *Tetrahedron Lett.*, in press.

H.C. Kolb, P.G. Andersson, and K.B. Sharpless, Towards an Understanding of the High Enantioselectivity in the Osmium Catalyzed Asymmetric Dihydroxylation (AD). Part 1: Kinetics, *J. Am. Chem. Soc.* in press.

FAX FROM

DR. ALFRED BADER
Suite 622
924 East Juneau Avenue
Milwaukee, Wisconsin 53202
Telephone: 414/277-0730
Fax: 414/277-0709

Date: March 6 96

To: Prof. K. Barry Sharpless
Fax: 619 784 7562

2 pages

Message:

Dear Barry

I have given the Adventures talk many, many times around the country, and enough is enough! Did I give you a copy of my Couper-Loschmidt paper to be published by Plenum? If not, I'll send it to you & you'll see what a great detective Anschütz was. No conceit in my family: its all in me — but that is a great talk.

Please help me with another matter: who are the great chemists now at MIT Dr. Schlögl should interview? See sample letter that follows.

Fond regards from house to house —

Alfred

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

March 5, 1996

Professor Satoru Masamune
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139

Dear Professor Masamune:

A very able historian of science, Dr. Reinhard Schlögl, of Radio Austria in Vienna, has been commissioned to produce a documentary on science at MIT.

Dr. Schlögl plans to visit MIT this coming May. He has asked me to contact some of the most eminent chemists at MIT to introduce him with the hope that he will be able to speak to you personally about your work.

With all good wishes, I remain,

Yours sincerely,

AB/cw

Barry:
I'd like to send such letters to about a dozen really able chemists at MIT

Thanks

THE SCRIPPS RESEARCH INSTITUTE

TELEFAX MESSAGE

DATE: March 5, 1996

FROM: K. Barry Sharpless
Fax Number (619) 784-7562
Phone Number (619) 784-7505

TO: [illegible]
Fax Number: 414 [illegible]
Phone Number: [illegible]

[illegible]

Dear [illegible]

Hope all is well in Milwaukee and that Spring is peeking in.

Lars, Ian and I have been working together on your San Diego lecture [illegible] extravaganza. We have you here at Scripps all day on Friday, April 26 with [illegible] lecture at 2 pm. You, Isabel and I will have a picnic lunch in the Torrey Pines State Park before your talk, if that is OK? Ian and others will join [illegible]

Finally, I have the unfortunate job of asking you to give us our "ta[illegible] lecture" ("The Adventures of a Chemist Collector"). I know it will be [illegible] time but a thoroughbred like you will take it in stride, right?

We all look forward to seeing you and Isabel soon.

[illegible]

K. Barry Sharpless

K. BARRY SHARPLESS
W. M. KECK PROFESSOR OF CHEMISTRY
TELEPHONE (619) 784-7505 • FAX (619) 784-
e-mail: sharpless@scripps.edu

Dr. Alfred Bader
924 East Juneau, Suite 622
Milwaukee, Wisconsin 53202
Phone: 414/277-0730
Fax: 414/277-0709

A Chemist Helping Chemists

May 24, 1996

Professor Barry Sharpless
Department of Chemistry
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, CA 92037

Dear Barry:

Just a hurried note before leaving for England and the Continent to tell you that I sent you beautiful portrait to a competent restorer in Minneapolis, Jim Horns, who told me that he hopes to have the work finished by August at a cost not to exceed $600.

He knows a good deal about paintings and likes a lot. So do I.

Of course, I told him to go ahead.

If you wish to reach me after talking to Michael Strem, you can call or fax me in Bexhill in Sussex at 011-44-1424-222223. We will be there until June 2nd and again from June 22nd through July 26th.

With best wishes from house to house,

AB/cw

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

November 5, 1992

Prof. K. C. Nicolaou
Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, California 92037

Dear KC:

I was so happy to note that you have won the A.C.S. Award for Creative work in Synthetic Organic Chemistry, sponsored by Aldrich.

Heartiest congratulations.

Sincerely,

c: Dr. Stephen Branca

THE SCRIPPS RESEARCH INSTITUTE
DEPARTMENT OF CHEMISTRY
10666 NORTH TORREY PINES ROAD
LA JOLLA, CALIFORNIA 92037
(619) 455-9100

November 25, 1992

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, WI 53211

Dear Alfred:

Your warm letter of congratulations made the ACS Award so much more meaningful and I thank you wholeheartedly for it! Hope to see you soon!

Cordially yours,

KC

K. C. Nicolaou, Chemistry Chairman
The Scripps Research Institute
and
Professor of Chemistry
University of California, San Diego

KCN/mjb

K.C. NICOLAOU, PH.D
CHAIRMAN AND DARLENE SHILEY PROFESSOR OF CHEMISTRY
TELEPHONE: (619) 554-3459 • FAX: (619) 554-6738

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

June 7, 1994

Professor K. Barry Sharpless
Scripps Research Institute
10666 N. Torrey Pines Road
La Jolla, California 92037

Dear Barry,

I haven't heard from you for the longest time and hope you are well.

Could you please glance over the enclosed page from my autobiography which deals with your paper for the Acta. Is my memory correct that you received over a thousand requests for reprints, or did you perhaps tell me that the Acta paper had over a thousand literature citations?

All good wishes from house to house.

As always,

Enclosure

We need not have worried about receiving enough papers. The prizes we established with the American Chemical Society, the Royal Institute of Chemistry and the Chemical Institute of Canada requested the winners to send us their award papers. Authors realized that the Acta's presentation of their papers was excellent and the distribution greater than that of any chemical journal. Also, the papers were abstracted by Chemical Abstracts and we provided free reprints. Barry Sharpless, one of America's most inventive chemists, told me that he received more requests for reprints of his Acta article--over 1000--than for any other paper he ever published. Not all the authors were well established chemists. In San Francisco we met Steven Gill, a young fellow with great enthusiasm about chemiluminescence. What he lacked in academic credentials he made up through practical experience and his paper was a gem. Of course Clint Lane who came to us from Herb Brown's lab wrote many fine papers on hydroboration, as did Chris Hewitt and Mike Silvester at Bristol Organics on fluoroaromatics. Many of our full page ads in the Acta were mini-review articles (fig. for 4).

Our first "dedicated" Acta, in 1977, honored Bob Woodward on his 60th birthday, and David Dolphin's article written partly seriously and partly tongue-in-cheek is one of the funniest biographical essays I have ever read. Other dedications to truly great chemists followed: Gilbert Stork, that gem of a teacher at Columbia for his 60th birthday; Herbert Brown, the father of Aldrich Boranes and so much more for his 75th, Ralph Raphael, Cambridge University's great father figure for his 65th, John Roberts, Cal Tech's inspired teacher for his 70th, and Albert Eschenmoser, one of a great succession of brilliant chemists at the ETH for his 65th birthday. In 1984 we published a Selections from the Aldrichimica Acta with the best papers published from 1967 to 1982, using the painting that had graced the Woodward Acta on its cover. Many

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

July 14, 1994

Professor and Mrs. K. B. Sharpless
Department of Chemistry
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, California 92037

Dear Jan and Barry,

Please accept my sincere thanks for your wonderful notes sent in early June.

Isabel and I were in Europe until a few days ago, and hence can thank you only now.

We much look forward to being in California for the A.C.S. meeting in April of next year, and hope to have a chance to thank you personally, then. By that time, I hope my autobiography will have been published. It talks about my many chemist friends around the world, and among them you are two of the best.

Fond regards.

Sincerely,

THE GARDEN OF THE VILLA MEDICI IN ROME
Diego Velázquez, Spanish, 1599–1660
Oil on canvas
Museo del Prado, Madrid

Published by
THE METROPOLITAN MUSEUM OF ART

11-00608-7
Printed in the U.S.A

6/10/94

Dear Alfred & Isabel,

I know Barry already wrote offering congratulations on the Parsons award, but I was just rereading the C&EN article before sending it on to Weslie Resnick Janeway, and I've got to write, too! Jock Whitney's motto was "make money, do good, live well," but I can't think of anyone to whom that applies better than you,

2

because Alfred made money doing good (Barry always says "Where would chemistry be without Alfred Bader?"), you use the money to do more good, and you live lives as full and rich and varied - and satisfying - as I can possibly imagine.

God bless you both

With much love,

Jan

THE SCRIPPS RESEARCH INSTITUTE
DEPARTMENT OF CHEMISTRY
10666 NORTH TORREY PINES ROAD
LA JOLLA, CALIFORNIA 92037
(619) 455-9100

June 2, 1994

Dr. Alfred and Isabel Bader
2961 North Shepard Avenue
Milwaukee, WI 53211

Dear Alfred and Isabel:

Jan and I so enjoyed the article in C&EN. What a wonderful partnership you two have and what a wonderfully full and rewarding life you continue--at full gallop, of course--to lead. We were delighted to read that you turned the disheartening end of your Sigma-Aldrich relationship into new opportunities and we're only sorry that we have no galleries in San Diego to lure you here.

But we can offer sunshine, comfortable accomodations (a lovely view of the ocean without getting out of bed), and good company. Jan has almost completed the total renovation of the house and gardens and we are looking forward to what we fear might be our last summer together as a family, since Hannah heads off to college in the fall.

Jan joins me in sending our very best wishes.

Sincerely yours,

K. Barry Sharpless

KBS:lcs

K. BARRY SHARPLESS, PH.D.
KECK PROFESSOR OF CHEMISTRY
TELEPHONE: (619) 554-7005 • FAX: (619) 554-6406

for Alfred and Isobel,
best wishes —
Barry

Pergamon

Tetrahedron Vol. 50, No. 15, pp. 4235-4258, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $6.00+0.00

0040-4020(94)E0067-4

Coelacanths and Catalysis*

K. Barry Sharpless

Department of Chemistry, The Scripps Research Institute
10666 North Torrey Pines Road, La Jolla, CA 92037

IN 1938, THREE YEARS BEFORE I WAS BORN, a live coelacanth was taken from the waters off the eastern coast of South Africa. Previously known only in the fossil record from some hundred million years ago, the coelacanth and the implications of its discovery remained big news for years, fueling an enthusiasm for "creatures" that persisted for decades. Those of us born in the Forties grew up on photos of eminent scientists setting off on expeditions, their sun-burnt faces dwarfed by mountain explorer's garb, or making thumbs-up signs as they entered the water in scuba gear. We shared their confident expectation that the Loch Ness Monster, Sasquatch, the Yeti — even a dinosaur — soon would be taken alive.

I grew up loving the sea and loving fishing in particular, but unlike most fishermen I cared less for the size or quantity of the catch than for its rarity. Nothing could be more exciting than pulling (if not this time, then surely the next!) a mysterious and hitherto unknown creature from the water. Clearly, I wanted to catch my own coelacanth.

Reports of fishing expeditions usually are scorned by scientific journals. However, Sir Derek Barton, Chairman of the Executive Board of Editors of Tetrahedron Publications, must take some responsibility for the nature of this article since he suggested it might be a rather personal review of my chemistry, including some of the background leading up to it: first of all, my background is awash with fish and fishing, specifically in the Manasquan River and that part of the Jersey Shore where the Manasquan meets the Atlantic Ocean; and secondly, I do chemistry the way I used to fish.

---

*Dedicated to four MIT colleagues: to Dan Kemp, who showed me how one should teach and taught me never to confuse opportunism with good science; to fellow fishermen Glenn Berchtold and George Büchi, who from the very first, starting with their generous mentoring when I was a novice faculty member, set an example that was and always has been worth emulating; and to Satoru Masamune, my all-time chalk-talk companion of choice.

As to the chemistry, upon looking through the contributions from Tetrahedron Prize recipients who preceded me at this honorable writing task, I realize they organized their chemical careers in terms of the different areas and the discrete projects in those areas on which they have worked. Essentially all my chemical investigations, however, are in only one area, and I tend to view my activity there not in terms of projects, but in terms of two passions I have had since graduate school and where those passions led me:

> I am passionate about the Periodic Table, and selenium, titanium and osmium became my favorite elements;
>
> I am passionate about catalysis, and, having laid a hand on two splendid examples of this elusive phenomenon, nothing else ever will be as stimulating.

What the ocean was to me as a child, the Periodic Table is to the chemist; new reactivity is, of course, my coelacanth.

Even though I grew up in Philadelphia, if someone asks me where I'm from I usually say "the Jersey Shore," because that's where my family spent summers, as well as many weekends and holidays, with my father joining us whenever he could. My father had a flourishing one-man general surgery practice which meant he was perpetually on call. With him at home so little and practically guaranteed to be called away when he was, my mother liked being near family and friends at the Shore, where her parents had settled and established a fishery after emigrating from Norway. When I was a baby, my parents bought a lot on a bluff overlooking the Manasquan River about four miles up from where the river enters the Atlantic.

Like many scientists I was a very shy child, happier and more confident when on my own. My interest was totally absorbed by the river. In those days the incoming tide transformed our part of the river from a channel flanked by broad mud flats to a quarter-mile basin that exploded with life of myriad variety — about a dozen kinds of fish big enough to make it to the dinner table, plus blue crab, eel, and a bounty of fry and fingerlings that would graduate downstream to the ocean. I was obsessed with finding and observing everything that lived in the river and knowing everyone who worked on it.

My most delicious childhood memory is the excitement I experienced the very moment I awoke on almost every summer morning; the sound I associate with that feeling is the distant whine of my first scientific mentor's outboard motor. That was my wake-up call, and within minutes I was at the river's edge, waiting in the pre-dawn stillness for Elmer Havens and his father Ollie to make their way across the river from Herbertsville to pick me up to "help" them seine for crabs. Amused by my regularly walking along the bank to watch them haul their seine, Elmer eventually installed me in the boat, which he used for transportation as well as for steadying himself as he dragged the seine's deep-water end. Ollie walked one end of the seine along the shore, alarming the crabs gathered at the river's edge, and frightening them toward deeper water and so into the net's pocket. Chest deep in water and mud, Elmer walked parallel to his father, one arm clasping the seine, the other hooked over the boat's gunwale. Elmer and I, our heads close together, would speculate about the catch, taking into account all the variables — the weather, the season, the tide. Every hundred yards or so, Elmer doubled ahead toward the shore to draw the purse. I liked it best if a big eel or a snapping turtle got caught up in the net, making the water boil and the net flop into the air. I always hoped we'd catch something new.

I had a little dinghy, and my realm of exploration expanded in direct proportion to my rowing ability. The same tide that created this abundant estuary also was my nemesis, forever stranding me upriver in the narrows or perhaps at Chapman's Boat Yard, a mile down river and on the opposite bank. Since my parents couldn't keep me off the water, they opted for increasing the likelihood of my getting home unaided by giving me a little boat with an outboard. It wasn't long before I went down river all the way to the inlet (absolutely forbidden, of course), and, soon after, the prospect of new creatures to pull from the water lured me out through the rock jetties and into the ocean: at the time I was only seven or perhaps eight years old.

By the time I was ten, I ran crab and eel traps and supplied everyone we knew with fish as well; at fourteen I started working during the summer as the first (and only) mate on a charter boat. My parents allowed me to start mating when I was so young and small even for my age because I was offered a job on a relative's boat — little did my parents or I know that Uncle Dink, a cousin actually, offered me the job so he wouldn't have to pay a "full-sized" helper. I so wanted to keep working on the boats that it was years before I dared tell my parents what went on aboard the *Teepee*, like how the Coast Guard refused assistance to Dink because his boat was in chronic disrepair. (Consequently, some of our adventures at sea were memorable indeed — grappling hooks and guns have their place in the canon — and I mention this trove of Uncle Dink stories because for years my MIT colleagues begged me to tell them over and over again.)

On a charter boat the captain pilots the ship and finds the fish the customers reel in. Meanwhile the mate is over the boat like a dervish, skillfully arraying the water with fishly temptations — adjusting outriggers, finding the perfect combination of lure or bait and tackle, always mindful of the action on nearby boats competing for the same fish.* Since my friends were all mates we naturally agreed that enticing fish to bite was the greatest challenge, but I alone felt that getting the strike was the most fun, even more exciting than landing the fish. I worked as a mate almost daily every summer, right up until the day before I set out from New Jersey headed toward the biggest ocean and graduate school at Stanford University.

That was in 1963. In the spring of that year my inspiring Dartmouth College chemistry professor and first research director, Tom Spencer, talked me into delaying entering medical school to try a year of graduate school. He sent me to Stanford specifically to work for E. E. van Tamelen, Tom's own mentor at Wisconsin. The appeal of fishing was such that Tom, to my later regret, never succeeded in getting me to spend any summers working in his lab. In fact even in graduate school I expressed my ambivalence by continuing to fantasize about finding a boat out of Manasquan to skipper and by failing — this did not please v.T. — to do the simple paperwork required to renew my NSF predoctoral fellowship.

However, toward the end of my first year at Stanford a serendipitous misunderstanding catalyzed the complete transfer of my passion (some would say my monomania) from one great science to another, from fishing to chemistry. Before leaving for a lengthy European visiting professorship, v.T. sent me to the library to look for reactive inorganic species that might produce interesting transformations of organic compounds. My first projects with v.T. were selective oxidation of polyolefins and titanium-mediated deoxygenative coupling of alcohols, and I was already primed to appreciate useful chemistry employing "strange" elements after selecting the Wittig Reaction from a list of suggested topics for my student seminar. The Wittig Reaction really engaged my enthusiasm, and I ingenuously concluded that finding new reactions other chemists could use looked like a lot of fun.

---

*This diversion into fishing-as-metaphor-for-research could go on for pages: consider how when a boat was hooking tuna — the catch of choice — word spread by radio and the competition converged from every compass point. The hot boat's captain greeted this acknowledgment of his success with some anxiety: while he liked setting the other captains' agendas and pleasurably speculating that the parties on the other boats were considering chartering him next time, the secrets of his success nonetheless required protection, so trolling speeds were lowered to sink the lures and prevent rubberneckers from identifying them, and red herrings (literally, on occasion!) were casually displayed on the fish box.

Isaak Walton and John Hersey devoted whole books to this metaphor, so indulge me for a few more sentences. The handy process *vs.* product dichotomy that applies so neatly to much of human endeavor illuminates this fisherman-chemist comparison, too. Conventional wisdom places fly-fishing at the "process" end of the scale, while a "product" fisherman uses sonar to find a school before he bothers to get his line wet. Process person though I am, only the Manasquan River ran through my fishing days: trolling for the unknown always had more appeal than hooking a trout I already knew was there.

In any event upon v.T.'s return I discovered he had not intended for me to spend *all* those months immersed in the literature. While I had no research results to report, I did have a notebook filled with ideas and an eagerness to drop my line throughout the vastness of the Periodic Table. I don't think I've gone fishing in the literal sense a dozen times since then!

From van Tamelen, a Gilbert Stork protégé, I inherited enthusiastic disdain for "safe" problems,* deep admiration for traditional multistep organic synthesis and awe before selective biological catalysis: studying the squalene oxide/lanosterol cyclase enzyme left me impressed by enzymic selectivity but depressed by the difficulty of using enzymes for synthetic transformations. After getting a double dose of him in the classroom, Derek Barton became my model. At Dartmouth Tom Spencer taught a course on conformational analysis based on one he took at Wisconsin from William S. Johnson (Tom's uncle, in fact), then I experienced the original at Stanford.† Being wet behind the ears I took conformational analysis for granted: it was Sir Derek's search for new reactivity that electrified me. A postdoc with Jim Collman (the only person, I concede, who gets more excited about chemistry than I do) ignited my interest in using simple metal complexes to develop catalysts (in the Collman lab, incidentally, I had the privilege of many hours at the blackboard with labmate Bob Grubbs). Then before taking up my job at MIT, a postdoc with Konrad Bloch confirmed my hunch that impatience rendered me incompetent around enzymes. Konrad graciously let me start working on my own ideas when his proved much too frustrating for me.

One other part of my background seems to have contributed to my chemistry. The first American Sharpless ("Sharples" then) came to Pennsylvania in the Seventeenth Century not long after William Penn. My father was a practicing Quaker only as a child, but the values in our home were Quaker values, and I was educated in a Quaker school. The Quakers encourage modesty, thrift, initiative and enterprise, but the greatest good is being a responsible member of the community — being useful. "Elegant" and "clever" were the chemical accolades of choice when I started doing research, just as "novel" is high praise now. Perhaps the Quakers are responsible for me valuing "useful" most.

So that, with apologies to Sir Derek for taking such advantage of his suggestion, is my background as a chemist. I've been accused of going too far when I speculate that chirality fascinates me because I handled my umbilical cord *in utero*, but I'm quite sincere in proposing that the extraordinary training I received as a young chemist transformed an existing passion for discovering the unknown into the search for new reactivity, and that Quaker utilitarianism made the selective oxidation of olefins so appealing.

With respect to chemical reactions, "useful" implies wide scope, simplicity to run, and an essential transformation of readily available starting materials. Clearly, if useful new reactivity is the goal, investigating the transformations chemists rely on is the obvious strategy. The processes for the selective oxidation of olefins have long been among the most useful tools for day-to-day organic synthesis because of these appealing characteristics of olefins:

they are among the cheapest functionalized organic starting materials,
they can be carried "hidden" through conventional acid/base-catalyzed transformations, then "revealed" at will by adding heteroatoms through selective oxidations,
most simple olefins are prochiral, providing a prominent portal to the chiral world.

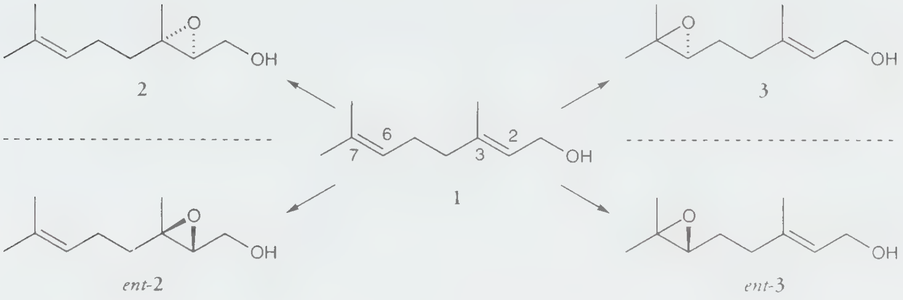
---

*Sat Masamune and Peter Dervan, fellow van Tamelen alumni, and I often discuss this shared legacy.

†When teaching MIT undergraduates I always said, "The lights came on with conformational analysis," without thinking where I picked up the phrase, but now I know: the previous Tetrahedron Prize article states, "Just as chemists of the Robinson generation worked without concern for stereochemical factors so we, in the early days, were working in ignorance of conformational considerations until Derek Barton showed us the light in 1950." The author is, of course, Bill Johnson.[1]

SCHEME I

Regio- and Enantioselective Monoepoxidations of Geraniol



The trisubstituted olefin geraniol, in addition to being one of my favorite smells, provides an excellent case study both for laying out the challenges of selective olefin oxidation as well as for noting some benchmarks in meeting those challenges.

As shown in scheme 1, geraniol has two trisubstituted olefinic units, one of which has a hydroxyl in the allylic position. Four monoepoxides are possible: making either racemic **2** or racemic **3** requires regio- (or chemo-) selectivity, while making each of the individual enantiomers requires enantioselectivity. When Henbest showed that the electronic deactivation by the oxygen substituent at C-1 causes peracids to prefer the 6,7-double bond (especially on the ester derivatives), making racemic **3** became possible.[2] When I started doing research in the Sixties, neither racemic **2** nor any of the enantiomers could be synthesized directly. Solving the other half of the regioselectivity problem was an obvious challenge, but enantioselectivity was considered well-nigh impossible.

In 1973 Bob Michaelson cracked the other half of the regioselectivity problem presented by geraniol.[3] Since early-transition-metal-catalyzed epoxidations with alkyl hydroperoxides proved highly selective for the 2,3-position, racemic **2** could be prepared as well.

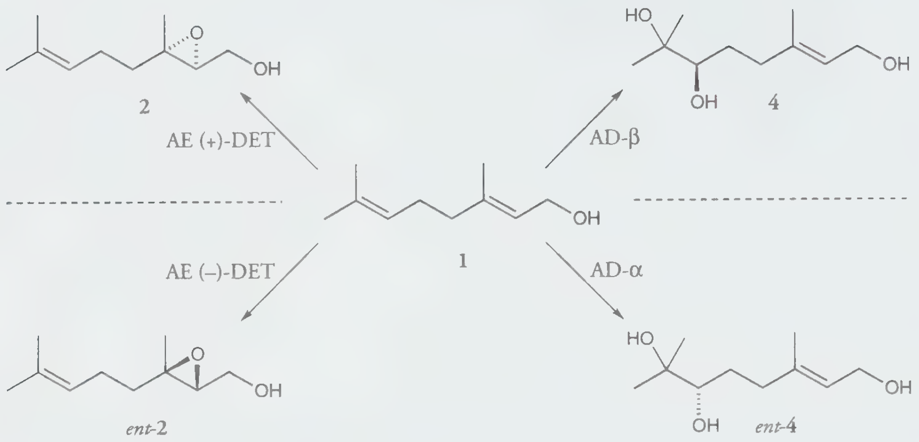
In 1980 Tsutomu Katsuki discovered the titanium-catalyzed asymmetric epoxidation (AE); the enantioselective oxidation of olefins bearing allylic hydroxyl groups made it possible to make either **2** or *ent*-**2** thus solving one side of the enantioselectivity problem.[4]

TABLE I

Some Widely-Used Catalytic Asymmetric Processes

Reported	Process
1968	Hydrogenation of functionalized olefins[7a,8a]
1978	Isomerization of allylic amines [8b,c,d]
1980	Titanium-catalyzed epoxidation of allylic alcohols [4,9a]
1988	Osmium-catalyzed dihydroxylation of isolated olefins [24,9b]
1990	Manganese-catalyzed epoxidation of isolated olefins [6,10]

SCHEME 2



The osmium-catalyzed asymmetric dihydroxylation (AD), discovered in 1987, subsequently was improved to the point that either **3** or *ent*-**3** could be made by way of the diol, an indirect solution to enantioselective epoxidation at the 6,7-position (scheme 2).[5]

In 1990 came the breakthrough introduction of enantioselectivity into existing salen ligand catalysts.[6] Eric Jacobsen's exciting manganese catalyst for isolated-olefin epoxidation came first and is still the leader, but the Jacobsen Epoxidation works best on only one of the six olefin-substitution classes. Nonetheless, its very existence is tantalizing, encouraging the hope that a general, off-the-shelf solution exists for the direct asymmetric epoxidation of the full range of isolated olefin substitution patterns.

The greater generality of man-made catalysts such as these compared with enzymes was noted first by Knowles[7a,c] and Kagan.[7b] During the lean times in the first decade of my career, their pioneering development of man's first highly enantioselective catalysts (the L-dopa synthesis that came out of Knowles' Monsanto lab was the asymmetric hydrogenation's first commercial application) sustained my faith that a catalyst for asymmetric oxidation could be found. Jack Halpern's mechanistic studies[7d] on asymmetric hydrogenation catalysis likewise inspired me. Several Japanese chemists, chief among them Ryoji Noyori,[7e] hugely extended both the scope and application of the asymmetric hydrogenation process.

This focused search has frustrated but never bored me even after so many years, and the geraniol paradigm illustrates why. My own investigations into the oxidation of olefins commenced at MIT in 1970, but, fittingly, I was back at Stanford on January 18, 1980, for Tsutomu Katsuki's dramatic discovery of the titanium-catalyzed asymmetric epoxidation.[4] Two years later the most scientifically stimulating and professionally gratifying collaboration of my career, the total syntheses of the eight L-hexoses with my MIT colleague Sat Masamune, capped the AE's discovery.[11] Previous articles[12] in a vein similar to this one describe that chemistry; understanding the AE's significance and putting that understanding to work are the purview here.

After the euphoria of completing the hexose syntheses, three years were spent developing, refining and finding more applications for the AE. During this time I returned to the search for new reactivity, but it was clear that my random, scattershot attempts were going nowhere,* so I was grateful for the opportunity to spend the first three months of 1987 as a Sherman Fairchild Scholar at Caltech.

Many universities and institutions have handsome Fairchild buildings, but Caltech, ever the bastion of collegiality and camaraderie, used its Fairchild grant to endow a program that brings scientists from many fields to be housed graciously in the sunshine for as long as a year. Since my research group's investigation of the AE had reached the point of diminishing returns, I left for Pasadena hoping to renew my mission.

I love reading journals, and I love mountains, so the Caltech library with its panoramic view of Mt. Wilson became my thinking place of choice. Every day Mt. Wilson offered new vistas, especially on those occasions when snow fell during the night. One morning the mountain was completely cloaked (the first time a freezing temperature was recorded in downtown LA, I recall), and the melting snow receded at such a clip I was sure I saw it happening. Mt. Wilson was the perfect backdrop for bringing my own big picture back into focus, and I returned to MIT eager to renew my search for new reactivity. Meditating on the AE yielded this lesson to guide that search:

> ligand-accelerated catalysis (the significance of which is documented in M. G. Finn's fine MIT thesis on the mechanism of the AE[13]), is crucial to the AE and not merely a feature of it; despite its rarity this phenomenon might be the agent for uncovering more catalytic processes

Of course the first and best-known example of ligand acceleration is found in Criegee's papers from the Thirties.[14] He observed that pyridine accelerates the reaction in his classic study of osmium tetroxide

---

*I have enormous admiration for colleagues who can keep multiple research projects alive and large groups humming, but the "monomania" that prevents me from being able to do that is my long suit as well, making it possible to concentrate — for years, actually — on a single topic. I know some chemists call my approach "intuitive," a term I've always thought underestimates the rigor that frames my method; perhaps "unstructured" or "contemplative" is more accurate. Many of my cohorts are quick and facile and can jump on a few interesting bits of data and start building tentative edifices that get taken apart and reassembled to suit new data. I, on the other hand, am ruminative: my training after all consisted of busily poking and perturbing the Manasquan River, a curriculum both urgent and leisurely, one that permitted exploration without assumptions and without the structure imposed by deadlines or competition or by knowing too little or too much. Since I was compelled by shyness to learn to do much on my own, there was (and is) no right or wrong way, only many ways, some more or less suited to a given endeavor. The discipline, nonetheless, is exacting: everything that can be observed should be observed, even if it is only recalled as the bland background from which the intriguing bits pop out like Venus in the evening sky. The goal is always finding something new, hopefully unimagined and, better still, hitherto unimaginable. When I became a bench- and desk-bound explorer the method stayed the same. I try to imagine away the packaging information arrives in, then let bits and pieces move around lazily, rather like objects tumbling slowly in zero gravity, but eventually, over time, exploring every possible relationship with other information that's previously arrived. Since joining the faculty of The Scripps Research Institute, I've discovered that ocean swimming and running on the beach provide an excellent medium for this kind of activity; however, in any climate the best catalyst is generous, stimulating conversation. This slow but endlessly fascinating method is like an exotic ritual courtship, full of displays of bright feathers or offerings of shiny metal or towers of sticks — what does it all, what does any of it mean? Enormous concentration is required to remember it all in a way that causes little sparks when certain conjunctions appear, making a connection with something noted previously, perhaps decades ago. Sadly, as I grow older, the connections become harder to summon up, so the sparks, though seeming as bright as ever, are less frequent. I describe this process at length because it's not the way most scientists approach their work, nor is it well suited to the demands of funding agencies that are railroaded into answering questions posed for political rather than scientific reasons, nor to the needs of graduate students who require publications to compete for jobs. Academic chemistry is much harder now, and I'm glad I was born when I was.

and olefins. Ironically, the lesson from the AE was directing me back toward Criegee, whose discoveries in olefin oxidation and osmylation were, in large measure, the jumping off point for my own research career.

I first looked into Criegee's process shortly after becoming an assistant professor at MIT. My attraction to the reaction of OsO_4 with olefins was inevitable. Osmium tetroxide not only accomplishes an important synthetic transformation, but it does so with a scope and reliability unique among reactions used for organic synthesis. It reacts *only* with olefins and it reacts with *all* olefins (slight poetic license here). Even R. B. Woodward valued Criegee's stoichiometric transformation so much he was willing to use 100 g of OsO_4 in one shot. Osmium's expense wasn't compatible with "useful," however and, since the existing catalytic variants were not very effective, I starting searching for a reliable catalytic method. In 1975 Kagayasu Akashi found a good process for us based on a hydroperoxide as oxidant, *tertiary*-butyl hydroperoxide (TBHP),[15] but the brass ring was ultimately captured that same year with the publication of the famous Upjohn process based on *N*-methyl morpholine-*N*-oxide (NMO).[16]

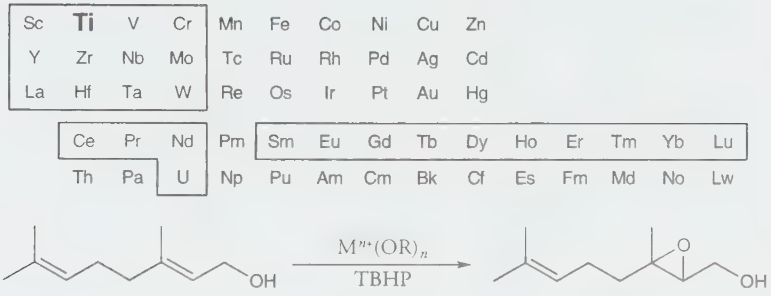
Throughout the rest of the Seventies osmium remained our primary tool for looking for new reactivity: we discovered that imido osmium(VIII) species effected stoichiometric *cis*-oxyamination of olefins in direct analogy to the *cis*-dihydroxylation of olefins by osmium tetroxide; even more effective catalytic versions of those transformations came shortly thereafter.

In 1977 I left MIT, where I had been a contented member of a wonderful chemistry faculty since 1970, for Stanford University, where I previously spent six contented years as a graduate student and post-doc, surrounded by a wonderful chemistry faculty. I never made the transition back to contentment at Stanford, probably because my research wasn't churning up much. This frustrated me and scared off potential graduate students who wanted publications, not a fishing expedition. In addition, at Stanford I remained awed by a faculty I worshiped when a graduate student, and I lacked the confidence to stand firm on issues, particularly faculty appointments, that meant a lot to me. In 1979 at about the same time I made the decision to return to MIT, Steve Hentges, who worked in our well-developed osmium imido area and already had the material for a good Ph.D. thesis in hand, decided to take on one more project before writing up.

The notion of an asymmetric ligand for osmium tetroxide had been knocking around the lab for years, and Steve first approached the idea by making several pyridines with chiral substituents at the 2-position; these gave diols with essentially 0% ee![17] Pyridine is only a modest ligand for osmium tetroxide, and we discovered any ortho substituent is lethal to binding. But since William Griffith at Imperial College showed that quinuclidine binds more strongly to OsO_4, I suggested trying the cinchona alkaloids, essentially substituted quinuclidines.[18] (Many chemists have expressed surprise at how quickly we arrived at what is now and may always be the best ligand framework for the AD: anyone with a natural products background and who is also a fan of Hans Wynberg's chemistry recognizes the cinchona alkaloids as the obvious next step.) The results were spectacular, even without taking into account a measurement error (discovered years later) that caused most of the ee's to be underreported by 5 to 15%![17]

Steve had a dramatic story to cap his thesis work, so he started writing; my attention was taken up by the decision to return to MIT: then a couple of months later Katsuki discovered an asymmetric process with ingredients so cheap it made working with osmium look like Rolls-Royce chemistry. Although the AE was only weakly catalytic in the early days,[19] its uniformly high ee's and nontoxic, inexpensive reagents were enough to completely divert our attention from its promising but stoichiometric predecessor, the OsO_4/cinchona asymmetric dihydroxylation.

The preceding paragraph has no doubt failed to deflect your attention from the obvious question: why didn't I try the Hentges ligands in the Upjohn system in 1979? Indeed, why did I propose the experiment in my NIH grant renewal in January, 1984, but not follow up on it? "As for the ligand," I wrote in



1

rac-2

FIGURE 1

Metals Catalyzing the Epoxidation of Allylic Alcohols by TBHP

Adding tartrate ligand *always* affects reactivity: the titanium system is accelerated; all twenty-four others are killed or dramatically slowed!

the proposal, "it is probably best to stay with the cinchona derivatives because the quinuclidine moiety is the best ligand we know of for Os(VIII) complexes. The substrate will be stilbene…the osmium catalyst will be recycled using an amine *N*-oxide. Ideally, both the osmium and the chiral alkaloid could be used in catalytic quantities. A successful system of this type could be of great practical importance."

Instead of poking and perturbing, the Jersey Shore School of Thinking's cardinal rule, I stuck with the odds logic suggested: ligands accelerate the reaction of OsO_4 with olefins, *but* they also bind avidly to the resulting osmate ester, lethally effecting catalyst turnover. This ability of ligands such as pyridine and quinuclidine to kill turnover in catalytic osmylation systems had been often observed in my laboratory. What I did not nor could not anticipate is the perfect balance cinchona alkaloids achieve in ligating ability, binding well enough to accelerate the key step, but weakly enough to slip off allowing the hydrolysis/reoxidation steps of the catalytic cycle to proceed. At the time, however, the precedents seemed clear, so the AD languished until 1987.

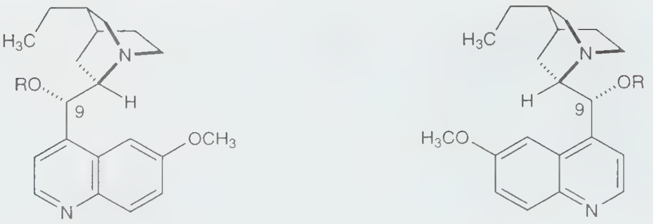
Unraveling the mechanism of the AE was largely the work of M. G. Finn.[13] His persistent exploration during the early- to mid-eighties of the AE's titanium-tartrate catalyst system exposed a complex mixture of species in dynamic equilibrium with one other.[20] M. G. discovered the main species $[Ti(DIPT)(O\text{-}i\text{-}Pr)_2]_2$ is substantially more active than the many other species present (significantly, it is five to ten times more active than $Ti(OR)_4$, a catalyst for the formation of racemic epoxy alcohol) and this rate advantage funnels catalysis through the appropriate tartrate-bearing species.

If the tartrate-induced acceleration of the titanium-catalyzed epoxidation reaction came as a surprise, investigating that phenomenon brought even more surprising results. We ultimately found twenty-four metals other than Ti that catalyze the epoxidation of allylic alcohols by TBHP (figure 1), but all these systems were strongly inhibited or killed by adding tartrate![21] Ligand-*de*celerated catalysis was clearly the rule while ligand *ac*celeration was the extraordinarily valuable exception.*

Shortly before I left for Caltech, Chris Burns, encouraged by Pui Tong Ho, presciently lobbied to resurrect the OsO_4/cinchona asymmetric dihydroxylation, and, without any encouragement from me I must admit, he embarked on the synthesis of a stoichiometric C_3-symmetric ligand for the AD.[22] A few

---

*For a detailed account of ligand-decelerated catalysis, see the discussion of the "tridentate fiasco" in reference 12a.



dihydroquinidine derivatives dihydroquinine derivatives

FIGURE 2
Cinchona Alkaloid Ligands for the Asymmetric Dihydroxylation (AD)

months later, I, too, was recommitted to osmium, and when Bill Mungall and Georg Schröder reviewed the work from 1979 they uncovered ee's even better than previously reported. Meanwhile Eric Jacobsen attacked the problem from the mechanistic side, discovering that the ligand-dependent rate accelerations could be enormous.[23]

With these very encouraging results on the stoichiometric reaction just in, Istvan Markó joined the project. I was travelling at the time, and on his own initiative, unaware of the NIH proposal, he combined Hentges' system[17] with the reliable Upjohn NMO-based catalytic osmylation system,[16] immediately getting results indicating the reaction was catalytic.[24] However, unlike the dramatic "Eureka!" that accompanied the discovery of the AE, cautious optimism was the response to the catalytic AD and its initially modest ee's. Now, however, after six years of research since Markó's first experiments in October of 1987, the AD's utility rivals and often surpasses the AE's.[9]

Unlike the AE, for which Katsuki's initial tartrate ester ligands have yet to be eclipsed, the ligands for the AD have evolved substantially in effectiveness and scope through substitution at the C-9 hydroxyl.

The simple ester derivatives (*e.g.* the acetate and *para*-chlorobenzoate esters) gave way in 1990 and 1991 to aryl ether derivatives, first proposed by Yun Gao during a late night group meeting to address the mechanistic question of a possible ligating role of the ester carbonyl. Brent Blackburn made the phenyl ether which, to our surprise, gave good ee's, but was too hard to make to be competitive (at least with the two aromatic olefins tried) with the then dominant *para*-chlorobenzoate (CLB) ligand.

Almost a year later Declan Gilheany correctly predicted that aryl ethers should be better for aliphatic olefins than the CLB ligand,[25] and these results laid the foundation for a steady expansion of this ligand class, culminating in the phenanthryl ether ligand.[26] Another big jump in effectiveness came with the dimeric alkaloid ligands having a phthalazine core, first made by Jens Hartung in 1990.[27] Along with the pyrimidine ligands[28] whose development they inspired, they remain the best general ligands for the AD reaction.

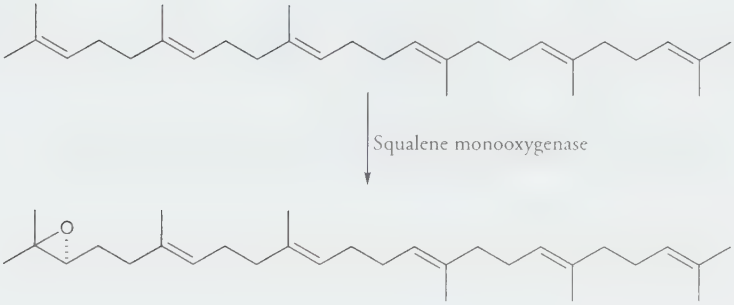
The search for better ligands has been paralleled by advances in catalyst turnover efficiency:

John Wai found both the second-catalytic-cycle problem and its partial remedy, slow addition of the olefin;[29]

Since ferricyanide in *tert*-butanol/water provides an excellent two-phase system for catalytic osmylation,[30] Hoi-Lun Kwong applied it to the AD solving the second-cycle problem and the need for slow addition;[31]

Willi Amberg found that adding organic sulfonamides greatly facilitates the rate of catalyst turnover for olefins whose osmate esters resist hydrolysis.[27]

SCHEME 3



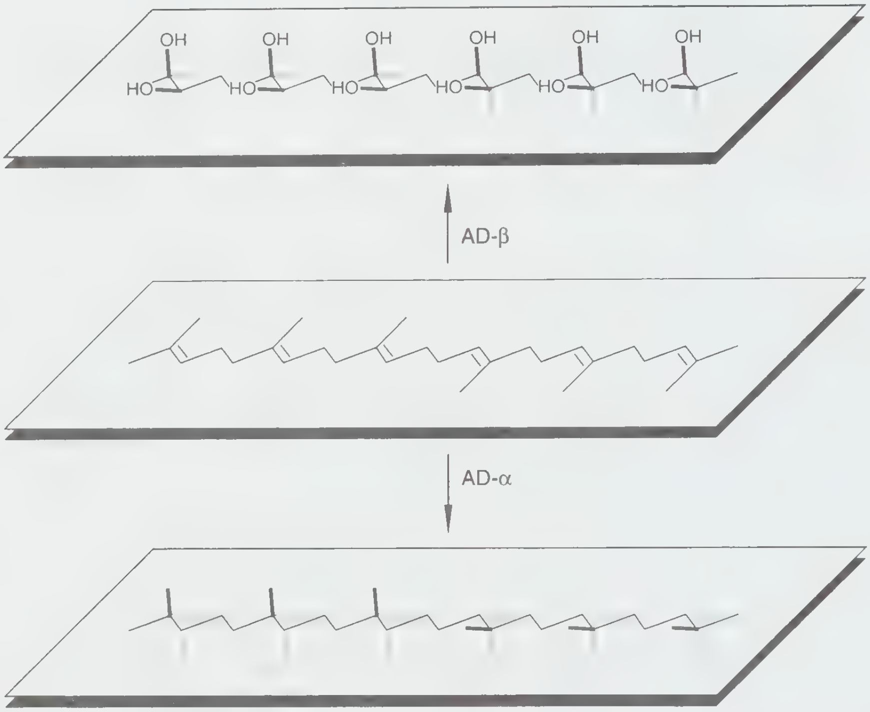
As the practicality (it has been scaled up to run in 4000 liter reactors with no ill effects on yield or ee[32]) and scope of the AD process grew, so did the pressure to understand the origin of its enantioselectivity. Mechanistic studies dating from the early Seventies by Alan Teranishi and Jan Bäckvall[33] were rekindled by Eric Jacobsen in 1987 and are now our major preoccupation. Some of the most important findings of the past three years will appear soon.[34]

While a complete and general solution to the geraniol paradigm's final challenge is tantalizingly within reach, comparing selectivity at the bench with selectivity in living systems remains striking. For example, the squalene monooxygenase in our livers unerringly deposits a single oxygen atom on the squalene molecule and, in so doing, further chooses only the *si*-enantioface of the terminal double bond (scheme 3).[35] On the other hand, the attempted AD of a single double bond of squalene does give the terminal diol in 96% ee. The preference for the terminal double bond is slight, however, and internal diols as well as tetraols also can be isolated from the reaction.[36] Thus while the AD catalyst cannot match the exquisite selectivity of the enzymic system, this very inability to discriminate between the six trisubstituted double bonds of squalene allows the exhaustive AD of squalene (scheme 4) in an overall yield of 79.8% for the AD-β reaction.[37]

Serial multistep reactions such as these are stymied by Bob Ireland's "arithmetic demon" — the geometric fall in yield in sequential chemical reactions. The AD of each double bond is one step in a procession of six dihydroxylations, each with a chemical and an optical yield, twelve yields in all. Thus the average yield of each step is $(0.798)^{1/12}$ or 98%, translating to 98% for each chemical yield, 96% ee for the single enantioselective reaction and 96% de for each of the five diastereoselective reactions. The high yield of a single enantiomer from the multiple hydroxylation events required to completely oxidize squalene reflects the reliability and selectivity of the AD process. Joel Hawkins' Berkeley lab kinetically resolved the chiral fullerene C_{76} resulting in the first enantiomerically pure allotrope of carbon, the AD's most intriguing use to date.[38]

My decision nearly twenty-five years ago to study the selective oxidation of olefins produced an unexpected bonus, one that gave me an opportunity to investigate uncharted territory on a scale that is more associated with the previous half-century than with our own. Selenium, titanium and osmium, my three most successful olefin oxidation catalysts, all had phobias associated with them that stunted their investigation. Selenium and osmium were considered highly toxic, and the peroxide oxidants used with titanium had a nasty reputation. Rarely did I find myself in another chemist's territory; likewise, few wanted to cast a line in mine.

SCHEME 4



Tracking these elements offers a rather curious way to view my research. Figure 3a plots the time course of their dominance (as measured by publications for want of a more qualitative ruler) during the past twenty-three years. Selenium came first, flourished, then ended abruptly. Osmium research came next, co-existing with selenium until both were eclipsed by titanium, the descendant of molybdenum and vanadium. Osmium made a strong comeback, knocking off titanium.

Figure 3b, charting my research with respect to catalytic transformations, looks quite unlike figure 3a, but relates directly to it. As my involvement with catalysis grew, the largely stoichiometric selenium reagents lost their appeal; titanium fell because the effectiveness of the titanium catalyst for the AE is modest, with about only twenty turnovers per titanium center before all activity is lost. Osmium, despite a bimodal presentation, was never actually out of the picture, merely quiescent until the discovery of the highly catalytic AD (it has been run to completion with as little as 1⁄50,000 of osmium catalyst).

In figure 3b the only real defection from the steady growth of catalysis to dominion in my research was the 1982 trough caused by the hexose synthesis collaboration with Sat Masamune. Stepping out of the realm of catalysis is almost unimaginable to me now, nor is osmium ever likely to be dislodged. Naturally I hope it will be joined by new catalysts.

Ultimately, catalysis and its power are the engine driving my research. With nature's catalysts for inspiration, it was possible to imagine small, asymmetric catalysts. Achieving that revealed the previously unimaginable: highly enantioselective catalysis without "lock and key" binding; small catalysts tolerating a wide range of substrates, thus with a high likelihood for synthetic utility; the notion of ligand-accelerated

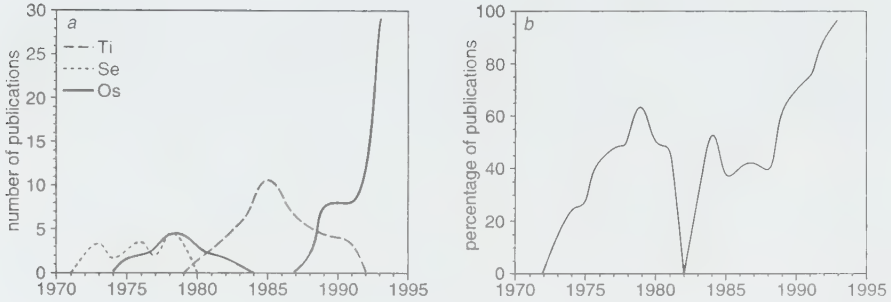


FIGURE 3
(a) Selenium, titanium and osmium chemistry; note the osmium line's bimodality.
(b) Growth of catalysis in my laboratory.

catalysis. The latter, I feel strongly, is the single most interesting finding to arise from the catalytic asymmetric epoxidation and dihydroxylation processes. Despite so far uncovering just these two ligand-accelerated systems and having identified a mere handful of others from the literature,[39] my research will continue to plumb the vastness of the Periodic Table for more examples: their potential for great utility overcomes my misgivings about their scarceness. I am, after all, the optimistic product of the generation that caught the coelacanth.

ACKNOWLEDGEMENT

Above all I thank and express my deep gratitude to my past and present coworkers at MIT, Stanford and The Scripps Research Institute. Many of you learned to tolerate my style of directing research (an oxymoron perhaps?); indeed, some of you flourished. Others were not well served, and to you I sincerely apologize. I'm exceedingly proud of you MIT undergraduates who got your feet wet in my lab and are embarking now on your own academic careers: remember you got your opportunities because Tom Spencer gave me mine and I expect you to do the same. Mentioning Tom brings me back, as so many things do, to E. E. van Tamelen: the bright flashes of his career remain of the first magnitude and still inspire me. And finally, my scientific career would have been unthinkable without the constant support and counsel of my wife, best friend — and ghost writer — Jan.

I also thank the National Institutes of Health (GM-28384) and the National Science Foundation (CHE-9296055) for their continuous financial support over the past twenty years, and more recently the William M. Keck Foundation for helping to make possible my present tenure at The Scripps Research Institute in La Jolla.

REFERENCES AND NOTES

1. Johnson, W.S. *Tetrahedron* **1991**, *47*, xi-1.
2. Henbest, H.B.; Wilson, R.A.L. *J. Chem. Soc.* **1957**, 1958.
3. Sharpless, K.B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
4. Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

5. (a) David Xu synthesized **4** and *ent*-**4** in 1991 during his work on the AD mechanism, from which synthesis of **3** and *ent*-**3** was implicit; two other groups reported this reaction sequence: (b) Corey, E.J.; Noe, M.C.; Shieh, W.C. *Tetrahedron Lett.* **1993,** *34,* 5995-5998; (c) Vidari, G.; Dapiaggi, A; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993,** *34,* 6485-6488; (d) Vidari, G.; Giori, A.; Dapiaggi, A; Lanfranchi, G. *Tetrahedron Lett.* **1993,** *34,* 6925-6928. Gerry Crispino's juvenile hormone III synthesis demonstrates the same conversion: (e) Crispino, G.A.; Sharpless, K.B. *Synthesis* **1993,** *8,* 777.
6. (a) Zhang, W.; Loebach, J.L.; Wilson, S.R. Jacobsen, E.N. *J. Am. Chem. Soc.* **1990,** *112,* 2801; (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990,** *31,* 7345.
7. (a) Knowles, W.S.; Sabacky, M.J. *J. Chem. Soc.; Chem. Commun.* **1968,** 1445; (b) Dang, T.P.; Kagan, H.B. *J. Chem. Soc.; Chem. Commun.* **1971,** 481 (c) Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D.; Weinkauff, D.J. *J. Am. Chem. Soc.* **1975,** *97,* 2567-2568. (d) See his excellent review: Halpern, J. *Science* **1982,** *217,* 401. (e) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980,** *102,* 7932-7934.
8. (a) Takaya, H.; Ohta, T. "Asymmetric Hydrogenation" In *Catalytic Asymmetric Synthesis,* Ojima, I. Ed.;VCH Publishers: New York, 1993; pp. 1-39; (b) Kumobayashi,H.; Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1978,** *100,* 3949; (c) Akutagawa, S.; Tani, K. "Asymmetric Isomerization of Allylamines" In *Catalytic Asymmetric Synthesis;* Ojima, I. Ed.;VCH Publishers, Inc.: New York, 1993; pp. 41-61. A history and review of the development of the asymmetric hydrogen migration of allylamines can be found in: (d) Otsuka, S.; Tani, K. *Synthesis* **1991,** 665-680.
9. For review chapters on both the AE and AD written largely by Roy Johnson despite being coauthored by both of us, see: (a) Johnson, R.A.; Sharpless, K.B. "Catalytic Asymmetric Epoxidation of Allylic Alcohols" In *Catalytic Asymmetric Synthesis*, Ojima, I. Ed.; VCH Publishers: New York, 1993; pp. 101-158; (b) Johnson, R.A.; Sharpless, K.B. "Catalytic Asymmetric Dihydroxylation" In *Catalytic Asymmetric Synthesis,* Ojima, I. Ed.; VCH Publishers: New York, 1993; pp. 227-272.
10. Jacobsen, E.N. "Asymmetric Catalytic Epoxidation of Unfunctionalized Olefins" In *Catalytic Asymmetric Synthesis,* Ojima, I. Ed.; VCH Publishers: New York, 1993; pp. 159-202.
11. (a) Ko, S.Y.; Lee, A.W.M.; Masamune, S.; Reed, L.A.; Sharpless, K.B.; Walker, F.J. *Science* **1983,** *220,* 949; (b) Ko, S.Y.; Lee, A.W.M.; Masamune, S.; Reed, L.A.; Sharpless, K.B.; Walker, F.J. *Tetrahedron* **1990,** *46,* 245.
12. (a) Sharpless, K.B. *CHEMTECH* **1985,** 692; (b) Sharpless, K.B. *Chem. Brit.* **1986,** *22,* 1.
13. M.G. Finn's thesis work has appeared in two full papers: (a) Woodard, S.S.; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991,** *113,* 106;(b) Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991,** *113,* 113.
14. (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936,** *522,* 75; (b) Criegee, R. *Angew. Chem.* **1937,** *50,* 153; (c) Criegee, R. *Angew. Chem.* **1938,** *51,* 519; (d) Criegee, R.; Marchand, B.; Wannowias, H. *Justus Liebigs Ann. Chem.* **1942,** *550,* 99.
15. Sharpless, K.B.; Akashi, K. *J. Am. Chem. Soc.* **1976,** *98,* 1986.
16. van Rheenen, V.; Kelly, R.C.; Cha, P.Y. *Tetrahedron Lett.* **1976,** 1973.
17. Hentges, S.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980,** *102,* 4263.
18 (a) Cleare, M.J.; Hydes, P.C.; Griffith, W.P.; Wright, M.J. *J. Chem. Soc., Dalton Trans.* **1977,** 941; (b) Griffith, W.P.; Skapski, A.C.; Woode, K.A.; Wright, M.J. *Inorg. Chim. Acta* **1978,** *31,* L413.
19. Five years later Bob Hanson made the simple but wonderful discovery that adding molecular sieves to the reaction dramatically increases catalyst turnover so that the AE process became truly catalytic: Hanson, R.M.; Sharpless, K.B. *J. Org. Chem.* **1986,** *51,* 1922.

20. Steve Pedersen provided invaluable structural results to aid M.G. Finn's studies during this period. Steve's work gave us our first glimpse into the dynamic world of complex mixtures in rapid equilibrium with each other. His contributions are summarized in: Sharpless, K.B. *Chemica Scripta (Sweden)* **1987,** *27,* 521. These studies led to no new catalysts, but they drove home our appreciation for the absolute need for a ligand-acceleration effect in catalyst systems where ligand exchange is rapid.
21. Kirshenbaum, K.S. Ph.D. Thesis, Massachusetts Institute of Technology, 1985.
22. Burns, C.J. Ph.D. Thesis, Massachusetts Institute of Technology, 1989.
23. Jacobsen, E.N.; Markó, E.I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989,** *111,* 737.
24. Jacobsen, E.N.; Markó, E.I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988,** *110,* 1968.
25. Shibata, T.; Gilheany, D.G.; Blackburn, B.K.; Sharpless, K.B. *Tetrahedron Lett.* **1990,** *31,* 3817.
26. Sharpless, K.B.; Amberg, W.; Beller, M.; Chen, H,; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991,** *56,* 4585.
27. Sharpless, K.B.; Amberg, W.; Bennani, Y.; Crispino, G.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang, Z.M.; Xu, D.; Zhang, X.L. *J. Org. Chem.* **1992,** *57,* 2768.
28. Crispino, G.; Jeong, K.S.; Kolb, H.; Wang, Z.M.; Xu, D.; Sharpless, K.B. *J. Org. Chem.* **1993,** *58,* 1958.
29. Wai, J.S.M.; Markó, I.; Svendsen, J.S.; Finn, M.G.; Jacobsen E.N.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989,** *111,* 1123.
30. Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990,** *55,* 766.
31. Kwong, H.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K.B. *Tetrahedron Lett.* **1990,** *31,* 2999.
32. Private communication from Dr. Yun Gao of Sepracor, Inc., Marlborough, MA.
33. Sharpless, K.B.; Teranishi, A.Y.; Bäckvall, J.E. *J. Am. Chem. Soc.* **1977,** *99,* 3120.
34. (a) Jacobsen, E.N.; Markó, E.I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989,** *111,* 737; (b) Göbel, T.; Sharpless, K.B. *Angew. Chem., Int. Ed. Eng.* **1993,** *32,* 1329; (c)Norrby, P.O.; Kolb, H., Sharpless, K.B. *Organometallics,* in press; (d) Kolb, H.C.; Andersson, P.G.; Bennani, Y.L.; Crispino, G.A.; Jeong, K.S.; Kwong, H.L.; Sharpless, K.B. *J. Am. Chem. Soc.*, in press; (e) Kolb, H.C; Andersen, P.G.; Sharpless, K.B. *J. Am. Chem. Soc.* in press; (f) Kwong, H.L. Ph.D. Thesis, Massachusetts Institute of Technology, 1993.
35. (a) Boar, R.B.; Damps, K. *Tetrahedron Lett.* **1974,** 3731; (b) Barton, D.H.R.; Jarman, T.R.; Watson, K.G.; Widdowson, D.A.; Boar, R.B.; Damps, K. *J. Chem. Soc., Chem. Commun.* **1974,** 861; (c) Barton, D.H.R.; Jarman, T.R.; Watson, K.G.; Widdowson, D.A.; Boar, R.B.; Damps, K. *J. Chem. Soc., Perkin I* **1975,** 1134.
36. Crispino, G.; Sharpless, K.B. *Tetrahedron Lett.* **1992,** *33,* 4273.
37. Crispino, G.A.; Ho, P.T.; Sharpless, K.B. *Science* **1993,** *259,* 64.
38. Hawkins, J.M.; Meyer, A. *Science* **1993,** *260,* 1918-1920.
39. With the help of my former postdoctoral coworkers Carsten Bolm and David Berrisford, I commenced writing some years ago a review of the ligand-acceleration phenomenon in catalysis. The article remains unfinished, but one beautiful example of the ligand-acceleration effect developed by the catalysis group at Ciba-Geigy Central Research deserves mention. All the ligand effects in that system are strikingly similar to the AD's, and yet their process involves a *heterogeneous* catalyst. In a production scale process, Ciba-Geigy asymmetrically hydrogenates α-ketoesters to lactate esters over a platinum catalyst modified by — cinchona alkaloid ligands! (a) Orito, Y.; Imai, S.; Niwa, S,; Nguyen, G.-H. *J. Synth. Org. Chem. Jpn.* **1979,** *37,* 173; (b) Orito, Y.; Imai, S.; Niwa, S, *J. Synth.*

Org. Chem. Jpn. **1979,** *37,* 1118; (c) Orito, Y.; Imai, S.; Niwa, S, *J. Synth. Org. Chem. Jpn.* **1980,** *38,* 670; (d) Orito, Y.; Imai, S.; Niwa, S, *J. Synth. Org. Chem. Jpn.* **1982,** *40,* 137; (e) Blaser, H.-U.; Jalett, H.P.; Wiehl, J. *J. Mol. Catal.* **1991,** *68,* 215-222; (f) Blaser, H.-U.; Jalett, H.P. "Enantioselective Hydrogenation of α-Ketoesters with Cinchona-Modified Platinum Catalysts" In *Heterogeneous Catalysis and Fine Chemicals III* Guisnet, M. Ed.; Elsevier: Amsterdam, 1993, pp 139-146. For a review, see: Blaser H.-U.; Müller, M. "Enantioselective Catalysis by Chiral Solids: Approaches and Results" In *Heterogeneous Catalysis and Fine Chemicals II* Guisnet, M. Ed.; Elsevier: Amsterdam, 1991, pp 73-92.

BIOGRAPHICAL SUMMARY

Born April 28, 1941, in Philadelphia, K. Barry Sharpless received his B.A. from Dartmouth College (1963), where Thomas Spencer introduced him to organic chemistry and to research, and his Ph.D. from Stanford University (1968) under the direction of E. E. van Tamelen and in collaboration with Raymond B. Clayton. After postdoctoral years with James P. Collman at Stanford and Konrad Bloch at Harvard, he joined the Massachusetts Institute of Technology faculty. After three years at Stanford in the late Seventies, he returned to MIT. He moved to The Scripps Research Institute in 1991 where he is the William M. Keck Professor of Chemistry.

A former Sloan Fellow, Dreyfus Teacher-Scholar, Guggenheim Fellow and Fairchild Scholar at the California Institute of Technology, Sharpless is a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences, and the American Association for the Advancement of Science. Honors include the American Chemical Society's Award for Creative Work in Organic Synthesis and the Arthur C. Cope Award, the Dr. Paul Janssen Prize (Belgium), the Allan R. Day Award (Philadelphia Organic Chemists Club), the Harrison Howe Award (Rochester Section, American Chemical Society), the Remsen Award (Maryland Section, American Chemical Society), the Prelog Medal (Eidgenössische Technische Hochschule, Zürich), the Rolf Sammet Prize (Goethe Universität, Frankfurt am Main), the Chemical Pioneer Award (American Institute of Chemists), the Scheele Medal (Swedish Academy of Pharmaceutical Sciences), and the Tetrahedron Prize for Creative Work in Organic Synthesis.

PUBLICATIONS

T.A. Spencer, M.A. Schwartz, and K.B. Sharpless, Synthesis of Resin Acid Intermediates. 8α,10β-Dimethyl-8-carbomethoxy-Δ^{19}-octalone-2, *J. Org. Chem.*, *29*, 782 (1964).

E.E. van Tamelen and K.B. Sharpless, Positional Selectivity During Controlled Oxidation of Polyolefins, *Tetrahedron Lett.*, *28*, 2655 (1967).

J.D. Willett, K.B. Sharpless, K.E. Lord, E.E. van Tamelen, and R.B. Clayton, Squalene-2,3-Oxide, an Intermediate in the Enzymatic Conversion of Squalene to Lanosterol and Cholesterol, *J. Biol. Chem.*, *242*, 4182 (1967).

E.E. van Tamelen, K.B. Sharpless, J.D. Willett, R.B. Clayton, and A.L. Burlingame, Biological Activities of Some Terminally Modified Squalene and Squalene 2,3-Oxide Analogs, *J. Am. Chem. Soc.*, *89*, 3920 (1967).

K.B. Sharpless, R.P. Hanzlik, and E.E. van Tamelen, A One-Step Synthesis of 1,5-Dienes Involving Reductive Coupling of Allyl Alcohols, *J. Am. Chem. Soc.*, *90*, 209 (1968).

E.E. van Tamelen, K.B. Sharpless, R.P. Hanzlik, R.B. Clayton, A.L. Burlingame, and, P.C. Wszolek, Enzymic Cyclization of *trans, trans, trans*-18,19-Dihydrosqualene 2,3-Oxide, *J. Am. Chem. Soc.*, *89*, 7150 (1967).

E.E. van Tamelen, R.P. Hanzlik, K.B. Sharpless, R.B. Clayton, W.J. Richter, and A.L. Burlingame, Enzymic Cyclization of 15-Norsqualene 2,3-Oxide, *J. Am. Chem. Soc.*, *90*, 3284 (1968).

K.B. Sharpless, Studies of the Mechanism of Action of 2,3-Oxidosqualene-Lanosterol Cyclase: Featuring Enzymic Cyclization of Modified Squalene Oxides, Ph.D. Dissertation, Stanford University (1968).

K.B. Sharpless, T.E. Snyder, T.A. Spencer, K.K. Maheshwari, G. Guhn, and R.B. Clayton, Biological Demethylation of 4,4-Dimethyl Sterols. Initial Removal of the 4α-Methyl Group, *J. Am. Chem. Soc., 90*, 6874 (1968).

K.B. Sharpless and E.E. van Tamelen, Terpene Terminal Epoxides. Skeletal Rearrangement Accompanying Bicyclization of Squalene 2,3-Oxide, *J. Am. Chem. Soc., 91*, 1848 (1969).

E.E. van Tamelen, B. Akermark, and K.B. Sharpless, Mechanism of the Titanium-Promoted Deoxygenative Coupling of Allyl and Benzyl Alcohols to Hydrocarbons, *J. Am. Chem. Soc., 91*, 1552 (1969).

R.J. Anderson, R.P. Hanzlik, K.B. Sharpless, and E.E. van Tamelen, Enzymic Transformation of an Acyclic Sesterterpene Terminal Epoxide to a Lanosterol Analog, *J. Chem Soc., Chem. Commun.*, 53 (1969).

K.B. Sharpless, T.E. Snyder, T.A. Spencer, K.K. Maheshwari, J.A. Nelson, and R.B. Clayton, Biological Demethylation of 4,4-Dimethyl Sterols. Evidence for Enzymic Epimerization of the 4β-Methyl Group Prior to Its Oxidative Removal, *J. Am Chem. Soc., 91*, 3394 (1969).

R. Rahman, K.B. Sharpless, T.A. Spencer, and R.B. Clayton, Removal of the 4,4-Dimethyl Carbons in the Enzymic Conversion of Lanosterol to Cholesterol: Initial Loss of the 4α-Methyl Group, *J. Biol. Chem., 245*, 2667 (1970).

K.B. Sharpless, Synthesis of *erythro*-18,19-Dihydroxysqualene 2,3-Oxide and Other Internally Oxidized Squalene Derivatives, *J. Chem Soc, Chem. Commun.*, 1450 (1970).

K.B. Sharpless, *d,l*-Malabaricane Diol. The First Cyclic Natural Product Derived from Squalene in a Nonenzymic Process, *J Am. Chem. Soc., 92*, 6999 (1970).

K.B. Sharpless and T.C. Flood, Oxotransition Metal Oxidants as Mimics for the Action of Mixed-Function Oxygenases "NIH Shift" with Chromyl Reagents, *J. Am. Chem. Soc., 93*, 2316 (1971).

K.B. Sharpless and R.F. Lauer, Oljan Repic, A.Y. Teranishi, and D.R. Williams, Permanganate in Acetic Anhydride. α-Diketones Directly from Olefins, *J. Am. Chem. Soc., 93*, 3303 (1971).

K.B. Sharpless, J.M. Townsend, and D.R. Williams, On the Mechanism of Epoxidation of Olefins by Covalent Peroxides of Molybdenum(VI), *J. Am. Chem. Soc., 94*, 295 (1972).

K.B. Sharpless and T.C. Flood, Direct Deoxygenation of Vicinal Diols with Tungsten (IV). A New Olefin Synthesis, *J. Chem Soc., Chem. Commun.*, 370, (1972).

K.B. Sharpless, M.A. Umbreit, M.T. Nieh, and T.C. Flood, Lower Valent Tungsten Halides. A New Class of Reagents for Deoxygenation of Organic Molecules, *J. Am. Chem. Soc., 94*, 6538 (1972).

J.M. Townsend and K.B. Sharpless, Mechanism of Decomposition of Sulfonium Betaines to Epoxides, *Tetrahedron Lett.*, 3313 (1972).

K.B. Sharpless and R.F. Lauer, Selenium Dioxide Oxidation of Olefins, Evidence for the Intermediacy of Allyl Seleninic Acids, *J. Am. Chem. Soc., 94*, 7154 (1972).

K.B. Sharpless and R.F. Lauer, Facile Thermal Rearrangements of Allyl Selenides and Diselenides. [1,3] and [2,3] Shifts, *J. Org. Chem., 37*, 3973 (1972).

K.B. Sharpless and A.Y. Teranishi, Chromyl Chloride in Acetone. α-Chloro Ketones or Ketones Directly from Olefins, *J Org. Chem., 38*, 185 (1973).

K.B. Sharpless and R.F. Lauer, A Mild Procedure for the Conversion of Epoxides to Allylic Alcohols. The First Organoselenium Reagent, *J. Am. Chem. Soc., 95*, 2697 (1973).

K.B. Sharpless, M.W. Young, and R.F. Lauer, Reactions of Selenoxides. Thermal *syn*-Elimination and $H_2^{18}O$ Exchange, *Tetrahedron Lett.*, 1979 (1973).

K.B. Sharpless and R.C. Michaelson, High Stereo- and Regioselectivities in the Transition Metal Catalyzed Epoxidations of Olefinic Alcohols by *t*-Butyl Hydroperoxide, *J. Am. Chem. Soc., 95*, 6136 (1973).

K.B. Sharpless, R.F. Lauer, and A.Y. Teranishi, Electrophilic and Nucleophilic Organoselenium Reagents. New Routes to α,β-Unsaturated Carbonyl Compounds, *J. Am. Chem. Soc., 95*, 6137 (1973).

D. Arigoni, A. Vasella, K.B. Sharpless, and H.P. Jensen, Selenium Dioxide Oxidations of Olefins. Trapping of the Allylic Seleninic Acid Intermediate as a Seleninolactone, *J. Am. Chem. Soc., 95*, 7917 (1973).

K.B. Sharpless and R.F. Lauer, Electrophilic Organoselenium Reagents. A New Route to Allylic Acetates and Ethers, *J. Org Chem., 39*, 429 (1974).

S. Tanaka, H. Yamamoto, H. Nozaki, K.B. Sharpless, R.C. Michaelson, and J.D. Cutting, Stereoselective Epoxidations of Acyclic Allylic Alcohols by Transition Metal-Hydroperoxide Reagents. Synthesis of *d,l*-C_{18} Cecropia Juvenile Hormone from Farnesol, *J. Am. Chem. Soc., 96*, 5254 (1974).

K.B. Sharpless and H.P. Jensen, Synthesis of a Novel Pentacoordinate Glyoxime Based Ligand and Preparation of its Chlorocobalt(III) Complex, *Inorg. Chem., 13*, 2617 (1974).

H.P. Jensen and K.B. Sharpless, An Improved Procedure for the Direct Oxidation of Olefins to α-Diketones by Potassium Permanganate in Acetic Anhydride, *J. Org. Chem.*, *39*, 2314 (1974).

H.P. Jensen and K.B. Sharpless, Selenium Dioxide Oxidation of *d*-Limonene—a Reinvestigation, *J. Org. Chem.*, *40*, 264 (1975).

K.B. Sharpless and M.W. Young, Olefin Synthesis. Rate Enhancement of the Elimination of Alkyl Aryl Selenoxides by Electron-Withdrawing Substituents, *J. Org. Chem.*, *40*, 947 (1975).

K.B. Sharpless, D.W. Patrick, L.K. Truesdale, and S.A. Biller, A New Reaction. Stereospecific Vicinal Oxyamination of Olefins by Alkyl Imido Osmium Compounds, *J. Am. Chem. Soc.*, *97*, 2305 (1975).

K.B. Sharpless, A.O. Chong, and J.A. Scott, Rapid Separation of Organic Mixtures by Formation of Metal Complexes, *J. Org. Chem.*, *40*, 1252 (1975).

K.B. Sharpless and D.R. Williams, The Reactions of Olefins with Permanganate, Ruthenium Tetroxide, and Osmium Tetroxide; Dependence of Rate on Degree of Substitution, *Tetrahedron Lett.*, 3045 (1975).

J.A. Nelson, S. Kahn, T.A. Spencer, K.B. Sharpless, and R.B. Clayton, Some Aspects of Substrate Specificity in Biological Demethylation at C4 of Steroids, *Bioorgan. Chem.*, *4*, 363 (1975).

K.B. Sharpless, K.M. Gordon, R.F. Lauer, D.W. Patrick, S.P. Singer, and M.W. Young, The Utility of Selenium Reagents in Organic Synthesis, *Chemica Scripta* (Sweden), Vol. 8A, 9 (1975).

K.B. Sharpless and Kageyasu Akashi, Oxidation of Alcohols to Aldehydes by Reagents Derived from Chromyl Chloride, *J Am. Chem. Soc.*, *97*, 5927 (1975).

K.B. Sharpless, T. Hori, L.K. Truesdale, and C.O. Dietrich, Allylic Amination of Olefins and Acetylenes by Imido Selenium Compounds, *J. Am. Chem. Soc.*, *98*, 269 (1976).

K.B. Sharpless and K.M. Gordon, Selenium Dioxide Oxidation of Ketones and Aldehydes. Evidence for the Intermediacy of β-Ketoseleninic Acids, *J. Am. Chem. Soc.*, *98*, 300 (1976).

K.B. Sharpless and T. Hori, Allylic Amination of Olefins and Acetylenes by Imido Sulfur Compounds, *J. Org. Chem.*, *41*, 176 (1976).

K.B. Sharpless, A.O. Chong, and K. Oshima, Osmium Catalyzed Oxyamination of Olefins by Chloramine-T, *J. Org. Chem.*, *41*, 177 (1976).

K.B. Sharpless and K. Akashi, Osmium Catalyzed Vicinal Hydroxylation of Olefins by *tert*-Butyl Hydroperoxide Under Alkaline Conditions, *J. Am. Chem. Soc.*, *98*, 1986 (1976).

K.B. Sharpless, K. Akashi, and K. Oshima, Ruthenium Catalyzed Oxidation of Alcohols to Aldehydes and Ketones by Amine-*N*-Oxides, *Tetrahedron Lett.*, 22503 (1976).

K.B. Sharpless and S.P. Singer, 1,2-Diamination of 1,3-Dienes by Imido Selenium Compounds, *J. Org. Chem.*, *41*, 2504 (1976).

R.C. Michaelson, R.E. Palermo, and K.B. Sharpless, Chiral Hydroxamic Acids as Ligands in the Vanadium Catalyzed Asymmetric Epoxidation of Allylic Alcohols by *tert*-Butyl Hydroperoxide, *J. Am. Chem. Soc.*, *99*, 1990 (1977).

A.O. Chong and K.B. Sharpless, On the Mechanism of the Molybdenum and Vanadium Catalyzed Epoxidation of Olefins by Alkyl Hydroperoxides, *J. Org. Chem.*, *42*, 1587 (1977).

K.B. Sharpless, A.Y. Teranishi, and J.-E. Bäckvall, Chromyl Chloride Oxidations of Olefins. Possible Role of Organometallic Intermediates in the Oxidations of Olefins by Oxotransition Metal Species, *J. Am. Chem. Soc.*, *99*, 3120 (1977).

A.O. Chong, K. Oshima, and K.B. Sharpless, Synthesis of Dioxo(*tert*-alkylimido)Osmium(VIII) and Oxotris(*tert*-alkylimido)Osmium(VIII) Complexes. Stereospecific Vicinal Diamination of Olefins, *J. Am. Chem. Soc.*, *99*, 3420 (1977).

M.A. Umbreit and K.B. Sharpless, Allylic Oxidation of Olefins by Catalytic and Stoichiometric Selenium Dioxide with *tert*-Butyl Hydroperoxide, *J. Am. Chem. Soc.*, *99*, 5526 (1977).

J.-E. Bäckvall, M.W. Young, and K.B. Sharpless, Vicinal Acetoxychlorination of Olefins by Chromyl Chloride in Acetyl Chloride, *Tetrahedron Lett.*, 3523 (1977).

T. Hori, S.P. Singer, and K.B. Sharpless, Allylic Deuteration and Tritiation of Olefins with *N*-Sulfinylsulfonamides, *J. Org. Chem.*, *43*, 1456 (1978).

S.P. Singer and K.B. Sharpless, Synthesis of *d,l*-Gabaculine Utilizing Direct Allylic Amination as the Key Step, *J. Org. Chem.*, *43*, 1448 (1978).

T. Hori and K.B. Sharpless, Synthetic Applications of Arylselenenic and of Arylseleninic Acids. Conversion of Olefins to Allylic Alcohols and to Epoxides, *J. Org. Chem.*, *43*, 1689 (1978).

K. Akashi, R.E. Palermo, and K.B. Sharpless, A Major Improvement in the Osmium Catalyzed Vicinal Hydroxylation of Olefins by *tert*-Butyl Hydroperoxide, *J. Org. Chem.*, *43*, 2063 (1978).

D.W. Patrick, L.K. Truesdale, S.A. Biller, and K.B. Sharpless, Stereospecific Vicinal Oxyamination of Olefins by Alkyl Imido Osmium Compounds, *J. Org. Chem., 43*, 2628 (1978).

T. Frejd and K.B. Sharpless, A New Rearrangement of *N*-Arylhydroxamic Acids Catalyzed by Seleninic Acids and Phenylselenenyl Chloride, *Tetrahedron Lett.*, 2239 (1978).

E. Herranz and K.B. Sharpless, Improvements in the Osmium Catalyzed Oxyamination of Olefins by Chloramine-T, *J. Org. Chem., 43*, 2544 (1978).

E. Herranz and S.A. Biller, and K.B. Sharpless, Osmium-Catalyzed Vicinal Oxyamination of Olefins by *N*-Chloro-*N*-Argentocarbamates, *J. Am. Chem. Soc., 100*, 3596 (1978).

L.S. Liebeskind, K.B. Sharpless, R. D. Wilson, and J.A. Ibers, The First d^0 Metallooxaziridines. Amination of Olefins, *J. Am Chem. Soc., 100*, 7061 (1978).

S. Current and K.B. Sharpless, Carbonyl Participation in the Addition of *p*-Chlorophenylselenenyl Bromide to (*E*)-4-Hexenal: A New Route to 2,6-Dideoxyglycosides, *Tetrahedron Lett.*, 5075 (1978).

J.-E. Bäckvall, K. Oshima, R.E. Palermo, and K.B. Sharpless, Some Reactions of *N*-(2-hydroxyalkyl)-*p*-toluenesulfonamides and *N*-allyl-*p*-toluenesulfonamides, *J. Org. Chem., 44*, 1953 (1979).

T. Hori and K.B. Sharpless, Conversion of Allylic Phenylselenides to the Rearranged Allylic Chlorides by *N*-Chlorosuccinimide. Mechanism of Selenium Catalyzed Allylic Chlorination of β–Pinene, *J. Org. Chem., 44*, 4208 (1979)

T. Hori and K.B. Sharpless, Selenium Catalyzed Non-Radical Chlorination of Olefins with *N*-Chlorosuccinimide, *J. Org. Chem., 44*, 4204 (1979).

B. Chabaud and K.B. Sharpless, Oxidation of Acetylenes with *tert*-Butyl Hydroperoxide Catalyzed by Selenium Dioxide α,α'-Dioxygenation of Internal Alkynes, *J. Org. Chem., 44*, 4202 (1979).

B.E. Rossiter, T.R. Verhoeven, and K.B. Sharpless, Stereoselective Epoxidation of Acyclic Allylic Alcohols. A Correction of Our Previous Work, *Tetrahedron Lett.*, 4733 (1979).

K.B. Sharpless and T.R. Verhoeven, Metal-Catalyzed, Highly Selective Oxygenations of Olefins and Acetylenes with *tert*-Butyl Hydroperoxide. Practical Considerations and Mechanisms, *Aldrichimica Acta, 12*, 63 (1979)

M.A. Umbreit and K.B. Sharpless, Deoxygenation of Epoxides with Lower Valent Tungsten Halides: *trans*-Cyclododecene, *Org. Syn.th, 60*, 29 (1981).

E. Herranz and K.B. Sharpless, Osmium-Catalyzed Vicinal Oxyamination of Olefins by *N*-Chloro-*N*-Metallocarbamates, *J Org. Chem., 45*, 2710 (1980).

S.G. Hentges and K.B. Sharpless, Asymmetric Induction in the Reaction of Osmium Tetroxide with Olefins, *J. Am. Chem Soc., 102*, 4263 (1980).

S.G. Hentges and K.B. Sharpless, Improved Procedure for the Oxyamination of Olefins with Trioxo(*tert*-butylimido)osmium(VIII), *J. Org. Chem., 45*, 2257 (1980).

T. Katsuki and K.B. Sharpless, The First Practical Method for Asymmetric Epoxidation, *J. Am. Chem. Soc., 102*, 5974 (1980)

E. Herranz and K.B. Sharpless, Osmium Catalyzed Vicinal Oxyamination of Olefins by Chloramine-T: *cis*-2-(*p*-Toluenesulfonamido)-cyclohexanol and 2-Methyl-3-(*p*-toluenesulfonamido)-2-pentanol, *Org. Synth., 61*, 85 (1983).

B.E. Rossiter, T. Katsuki, and K.B. Sharpless, Asymmetric Epoxidation Provides Shortest Routes to Four Chiral Epoxy Alcohols which are Key Intermediates in Syntheses of Methymycin, Erythromycin, Leukotriene C-1 and Disparlure, *J. Am Chem. Soc., 103*, 464 (1981).

D.J. Morgans, K.B. Sharpless, and S.G. Traynor, Epoxy Alcohol Rearrangements: Hydroxyl Mediated Delivery of Lewis Acid Promoters, *J. Am. Chem. Soc., 103*, 462 (1981).

E. Herranz and K.B. Sharpless, Osmium Catalyzed Vicinal Oxyamination of Olefins by *N*-Chloro-*N*-Argento-Carbamates *threo-N*-(1-Hydroxy-1,2-Diphenyl-2-yl) Ethyl Carbamate, *Org. Synth., 61*, 93 (1981)

P.H.J. Carlsen, T. Katsuki, V.S. Martin, and K.B. Sharpless, A Greatly Improved Procedure for Ruthenium Tetroxide-Catalyzed Oxidations of Organic Compounds, *J. Org. Chem., 46*, 3936 (1981).

V.S. Martin, S.S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K.B. Sharpless, Kinetic Resolution of Racemic Allylic Alcohols by Enantioselective Epoxidation. A Route to Substances of Absolute Enantiomeric Purity?, *J. Am. Chem. Soc., 103*, 6237 (1981)

T. Katsuki, A.W.M. Lee, P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, D. Tuddenham, and F.J. Walker, Synthesis of Saccharides and Related Polyhydroxylated Natural Products 1: Simple Alditols, *J. Org. Chem., 47*, 1373 (1982).

P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, S.M. Viti, Synthesis of Saccharides and Related Polyhydroxylated Natural Products 2: Simple Deoxyalditols, *J. Org. Chem., 47*, 1378 (1982).

A.W.M. Lee, V.S. Martin, S. Masamune, K.B. Sharpless, and F.J. Walker, Synthesis of Saccharides and Related Polyhydroxylated Natural Products 3: Efficient Conversion of 2,3-*erythro*-Aldoses to 2,3-*threo*-Aldoses, *J. Am. Chem. Soc., 104*, 3515 (1982).

M.A. Warpehoski, B. Chabaud, and K.B. Sharpless, Selenium Dioxide Oxidation of Endocyclic Olefins. Evidence for a Dissociation-Recombination Pathway, *J. Org. Chem., 47*, 2897 (1982).

N.C. Gonnella, K. Nakanishi, V.S. Martin, and K.B. Sharpless, General Method for Determining Absolute Configurations of Acyclic Allylic Alcohols, *J. Am. Chem. Soc., 104*, 3775 (1982).

K.B. Sharpless, C.H. Behrens, T. Katsuki, A.W.M. Lee, V.S. Martin, M. Takatani, S.M. Viti, F.J. Walker, and S.S. Woodard, Stereo- and Regioselective Openings of Chiral 2,3-Epoxy Alcohols. Versatile Routes to Optically Pure Natural Products and Drugs. Unusual Kinetic Resolutions., *Pure and Applied Chemistry, 55*, 589 (1983).

L.A. Reed, Y. Ito, S. Masamune, and K.B. Sharpless, Synthesis of Saccharides and Related Polyhydroxylated Natural Products. 4. α-D-and β-D-C-Glycopyranosides (2,6-Dialkyl-Substituted Tetrahydropyrans), *J. Am. Chem. Soc.*, 104, 6468 (1982).

S.Y. Ko, A.W.M. Lee, S. Masamune, L.A. Reed, K.B. Sharpless, and F.J. Walker, Total Synthesis of the *L*-Hexoses, *Science, 220*, 949 (1983).

J.G. Hill, B.E. Rossiter, and K.B. Sharpless, Anhydrous *tert*-Butyl Hydroperoxide in Toluene. The Preferred Reagent for Applications Requiring Dry TBHP., *J. Org. Chem., 48*, 3607 (1983).

S. Miyano, L.D.L. Lu, S.M. Viti, and K.B. Sharpless, Kinetic Resolution of Racemic β-Hydroxyamines by Enantioselective *N*-Oxide Formation., *J. Org. Chem., 48*, 3608 (1983).

K.B. Sharpless, S.S. Woodard and M.G. Finn, On the Mechanism of Titanium-Tartrate Catalyzed Asymmetric Epoxidation, *Pure and Appl. Chem.*, 55, 1823 (1983).

C.H. Behrens and K.B. Sharpless, New Transformations of 2,3-Epoxy Alcohols and Related Derivatives. Easy Routes to Homochiral Substances, *Aldrichimica Acta, 16*, 4 (1983).

L.D.L. Lu, R.A. Johnson, M.G. Finn, and K.B. Sharpless, Two New Asymmetric Epoxidation Catalysts. Unusual Stoichiometry and Inverse Enantiofacial Selection, *J. Org. Chem., 49*, 728 (1984).

K.B. Sharpless, Discovery of the Titanium-Catalyzed Asymmetric Epoxidation—A Personal Account., *Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research XXVII Stereospecificity in Chemistry and Biochemistry*, November 7-9, 1983, Houston, Texas, 1984.

B.E. Rossiter and K.B. Sharpless, Asymmetric Epoxidation of Homoallylic Alcohols. Synthesis of (–)-γ-Amino-β-(*R*)-Hydroxybutyric Acid (GABOB). *J. Org. Chem., 49*, 3707 (1984).

J.M. Hawkins and K.B. Sharpless, *threo-N,N'*-Bis (α-methylbenzyl) sulfamide: A Readily Available Chiral Ligand for Asymmetric Lithium Aluminum Hydride Reductions. *J. Org. Chem., 49*, 3861, (1984).

I.D. Williams, S.F. Pedersen, K.B. Sharpless, and S.J. Lippard, Crystal Structures of Two Titanium Tartrate Asymmetric Epoxidation Catalysts, *J. Am. Chem. Soc., 106*, 6430 (1984).

J.G. Hill, K.B. Sharpless, C.M. Exon, and R. Regenye, Enantioselective Epoxidation of Allylic Alcohols: (*2S,3S*)-3-Propyloxiranemethanol, *Org. Synth., 63*, 66 (1984).

C.E. Adams, F.J. Walker, and K.B. Sharpless, Enantioselective Synthesis of Swainsonine, A Trihydroxylated Indolizidine Alkaloid, *J. Org. Chem., 50*, 420 (1985).

K.B. Sharpless, A New Strategy For Full Control of Relative Stereochemistry Expands the Role of Asymmetric Synthesis, *Chemica Scripta* (Sweden), *25*, 71 (1985).

M.G. Finn, and K.B. Sharpless, On the Mechanism of Asymmetric Epoxidation with Titanium-Tartrate Catalysts, "Asymmetric Synthesis," Vol. 5, James D. Morrison, Ed.; Academic Press, Inc., New York, (1985), Chapter 8, pp. 247-308.

J.M. Klunder, M. Caron, M. Uchiyama, and K.B. Sharpless, Chlorohydroxylation of Olefins with Peroxides and Titanium Tetrachloride, *J. Org. Chem., 50*, 912 (1985).

K.S. Kirshenbaum and K.B. Sharpless, Improved Procedure for the Tungstate-catalyzed Epoxidation of α,β-Unsaturated Acids, *J. Org. Chem., 50*, 1979 (1985).

M.J. Schweiter and K.B. Sharpless, The Asymmetric Epoxidation of *tert*-Butyl Substituted Allylic Alcohols, *Tetrahedron Lett.*, 2543 (1985).

M. Caron and K.B. Sharpless, $Ti(O\textit{i}Pr)_4$-Mediated Nucleophilic Openings of 2,3-Epoxy Alcohols. A Mild Procedure for Regioselective Ring-Opening, *J. Org. Chem., 50*, 1557 (1985).

J.M. Chong and K.B. Sharpless, Nucleophilic Opening of 2,3-Epoxy Acids and Amides Mediated by $Ti(O\textit{i}Pr)_4$. Reliable C-3 Selectivity, *J. Org. Chem., 50*, 1560 (1985).

S. Miyano, L.D.L. Lu, S.M. Viti and K.B. Sharpless, Kinetic Resolution of Racemic β–Hydroxyamines by Enantioselective *N*-Oxide Formation, *J. Org. Chem., 50*, 4350 (1985).

J.M. Chong and K.B. Sharpless, Regioselective Openings of 2,3-Epoxy Acids with Organocuprates, *Tetrahedron Lett.*, 4683 (1985).

C.H. Behrens, S.Y. Ko, F.J. Walker, and K.B. Sharpless, Selective Transformation of 2,3-Epoxy Alcohols and Related Derivatives. Strategies for Nucleophilic Attack at Carbon-1, *J. Org. Chem.*, *50*, 5687 (1985).

C.H. Behrens and K.B. Sharpless, Selective Transformations of 2,3-Epoxy Alcohols and Related Derivatives. Strategies for Nucleophilic Attack at Carbon-3 or Carbon-2, *J. Org. Chem.*, *50*, 5696 (1985).

T. Katsuki and K.B. Sharpless, Method for Asymmetric Epoxidation, U.S. Patent 4,471,130, 1984, assigned to Stanford University.

K.B. Sharpless, The Discovery of Titanium-Catalyzed Asymmetric Epoxidation, *CHEMTECH*, 692 (1985)

J.M. Hawkins, J.C. Dewan, and K.B. Sharpless, Dioxomolybdenum(VI)-Substituted 2,6-Pyridinedimethanol Complexes: New Five-Coordinate Species, *Inorg. Chem.*, *25*, 1501 (1986).

K.B. Sharpless, The Discovery of the Asymmetric Epoxidation, *Chem. Brit.*, *22*, 1 (1986).

R.M. Hanson and K.B. Sharpless, Procedure for the Catalytic Asymmetric Epoxidation of Allylic Alcohols in the Presence of Molecular Sieves, *J. Org. Chem.*, *51*, 1922 (1986).

K.B. Sharpless and R.A. Johnson, Metal-Mediated Halohydrin Formation, U. S. Patent 4,560,811, 1985, assigned to the Massachusetts Institute of Technology.

J.M. Klunder, S.Y. Ko, and K.B. Sharpless, Asymmetric Epoxidation of Allyl Alcohol: Efficient Routes to Homochiral β-Adrenergic Blocking Agents, *J. Org. Chem.*, *51*, 3710 (1986).

K.S. Kirshenbaum and K.B. Sharpless, Regioselective Nucleophilic Opening of *erythro-* and *threo*-2,3 Epoxy Alcohols, *Chem. Lett.*, 11 (1987).

Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H. Masamune, and K.B. Sharpless, Catalytic Asymmetric Epoxidation and Kinetic Resolution: Modified Procedures Including In Situ Derivatization, *J. Am. Chem. Soc.*, *109*, 5765 (1987)

S.Y. Ko and K.B. Sharpless, *In Situ* Opening of Epoxy Alcohols: A Convenient Alternative to the Isolation of Unstable Epoxy Alcohols, *J. Org. Chem.*, *51*, 5413 (1986).

K.B. Sharpless, Architecturally Interesting Metal Complexes with Thermodynamically Dictated Structures, *Chemica Scripta* (Sweden), *27*, 521 (1987).

S.Y. Ko, H. Masamune, and K.B. Sharpless, *p*-Nitrobenzoate Esters of Epoxy Alcohols: Convenient Synthons for Water-Soluble Epoxy Alcohols, *J. Org. Chem.* *52* , 667 (1987).

A.D. Elbein, T. Szumilo, B.A. Sanford, K.B. Sharpless, and C.E. Adams, Effect of Isomers of Swainsonine on Glycosidase Activity and Glycoprotein Processing, *Biochemistry*, *26*, 2502 (1987)

S.F. Pedersen, J.C. Dewan, R.R. Eckman, and K.B. Sharpless, Unexpected Diversity in the Coordination Chemistry of Tartrate Esters with Titanium(IV), *J. Am. Chem. Soc.*, *109*, 1279 (1987).

J.M. Klunder and K.B. Sharpless, A Convenient Synthesis of Sulfinate Esters from Sulfonyl Chlorides, *J. Org. Chem.*, *52*, 2598 (1987).

J.M. Hawkins and K.B. Sharpless, Asymmetric Epoxidation Models: An Alkyl Hydroperoxide Dependent Change in Mechanism, *Tetrahedron Lett.*, *28*, 2825 (1987).

E.N. Jacobsen, I. Markó, W.S. Mungall, G. Schröder, and K.B. Sharpless, Asymmetric Dihydroxylation *via* Ligand-Accelerated Catalysis, *J. Am. Chem. Soc.*, *110*, 1968 (1988).

K.B. Sharpless, Catalytic Asymmetric Epoxidation, *Janssen Chimica Acta*, *6*, 3 (1988).

P. Carlier, W.S. Mungall, G. Schröder, and K.B. Sharpless, Enhanced Kinetic Resolution and Enzyme-Like Shape Selectivity, *J. Am. Chem. Soc.*, *110*, 2978 (1988).

C. Bolm, W.M. Davis, R.L. Halterman, and K.B. Sharpless, Synthesis and Crystal Structure of a Chiral C_3-Symmetric Monophosphine, *Angew. Chem., Int. Ed. Engl.*, *27*, 835 (1988).

Y. Gao and K.B. Sharpless, $Ti(O\text{-}i\text{-}Pr)_4$-Mediated Formation of 2,3-Epithio Alcohols from 2,3-Epoxy Alcohols, *J. Org. Chem.*, *53*, 4114 (1988).

Y. Gao and K.B. Sharpless, Asymmetric Synthesis of Both Enantiomers of Tomoxetine and Fluoxetine. Selective Reduction of 2,3-Epoxycinnamyl Alcohol with Red-Al, *J. Org. Chem.*, *53*, 4081 (1988).

M. Caron, P.R. Carlier, and K.B. Sharpless, Regioselective Azide Opening of 2,3-Epoxy Alcohols by $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$: Synthesis of α-Amino Acids, *J. Org. Chem.*, *53*, 5185 (1988).

C. Bolm and K.B. Sharpless, Synthesis of a C_3-Symmetric Phospha[2.2.2] Cyclophane, *Tetrahedron Lett.*, *29*, 5101 (1988)

Y. Gao and K.B. Sharpless, Vicinal Diol Cyclic Sulfates: Like Epoxides Only More Reactive, *J. Am. Chem. Soc., 110,* 7538 (1988).

J.M. Klunder, T. Onami, and K.B. Sharpless, Arenesulfonate Derivatives of Homochiral Glycidol: Versatile Chiral Building Blocks for Organic Synthesis, *J. Org. Chem., 54,* 1295 (1989).

E.N. Jacobsen, I. Markó, M.B. France, J.S. Svendsen, and K.B. Sharpless, Kinetic Role of the Alkaloid Ligands in Asymmetric Catalytic Dihydroxylation, *J. Am. Chem. Soc., 111,* 737 (1989).

J.S.M. Wai, I. Markó, J.S. Svendsen, M.G. Finn, E.N. Jacobsen and K.B. Sharpless, A Mechanistic Insight Leads to a Greatly Improved Osmium-Catalyzed Asymmetric Dihydroxylation Process, *J. Am. Chem. Soc., 111,* 1123 (1989).

S.Y. Ko, A.W.M. Lee, S.A. Masamune, L.A. Reed, III, K.B. Sharpless, and F.J. Walker, Total Synthesis of the L-Hexoses, *Tetrahedron, 46,* 245 (1990).

W. Bartmann and K.B. Sharpless, eds., "Stereochemistry of Organic and Bioorganic Transformations," VCH Verlagsgesellschaft, Weinheim, 1987.

B.B. Lohray, Y. Gao and K.B. Sharpless, One Pot Synthesis of Homochiral Aziridines and Aminoalcohols from Homochiral 1,2-Cyclic Sulfates, *Tetrahedron Lett., 30,* 2623 (1989).

J.S. Svendsen, I. Markó, E.N. Jacobsen, Ch. P. Rao, S. Bott and K.B. Sharpless, On the Structure of Osmium Tetroxide-Cinchona Alkaloid Complexes, *J. Org. Chem., 54,* 2263 (1989).

B.B. Lohray, T.H. Kalantar, B.M. Kim, C.Y. Park, T. Shibita, J.S.M. Wai and K.B. Sharpless, Documenting the Scope of the Catalytic Asymmetric Dihydroxylation, *Tetrahedron Lett., 30,* 2041 (1989).

B.M. Kim and K.B. Sharpless, Cyclic Sulfates Containing Acid-Sensitive Groups and Chemoselective Hydrolysis of Sulfate Esters, *Tetrahedron Lett., 30,* 655, (l989).

C.J. Burns, C.A. Martin, and K.B. Sharpless, Tartrate-Like Ligands in the Asymmetric Epoxidation, *J. Org. Chem., 54,* 2826 (1989).

P.R. Carlier and K.B. Sharpless, Studies on the Mechanism of the Asymmetric Epoxidation: A Ligand Variation Approach, *J Org. Chem., 54,* 4016 (1989).

G.D.H. Dijkstra, R.M. Kellogg, and H. Wynberg; J.S. Svendsen, I. Markó and K.B. Sharpless, Conformational Study of Cinchona Alkaloids. A Combined NMR, Molecular Mechanics and X-Ray Approach, *J. Am. Chem. Soc., 111,* 8069 (1989).

K.B. Sharpless and I.E. Markó, Ligand-Accelerated Catalytic Asymmetric Dihydroxylation using Dihydroquinidine and Dihydroquinidine Esters as Ligands, U.S Patent 4,871,855, 1989 assigned to the Massachusetts Institute of Technology.

M. Hayashi, F. Okamura. T. Toba, N. Oguni. and K.B. Sharpless, Kinetic Resolution of Racemic β–Hydroxy Amines by Enantioselective N-Oxide Formation, *Chem. Lett., 547* (1990).

R.M. Pearlstein, B.K. Blackburn, W.M. Davis, and K.B. Sharpless, Structural Characterization of the Pseudoenantiomeric *Cis*-Dioxo Osmium(VI) Esters of Chiral Diols with Cinchona Alkaloid Ligands, *Angew. Chem., Int. Ed. Engl., 29,* 639, (1990).

H. Kwong, C. Sorato, Y. Ogino, H. Chen, and K.B. Sharpless, Preclusion of the "Second Cycle" in the Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins Leads to a Superior Process, *Tetrahedron Lett., 31,* 2999, (1990).

B. Moon Kim and K.B. Sharpless, Heterogeneous Catalytic Asymmetric Dihydroxylation: Use of a Polymer-Bound Alkaloid, *Tetrahedron Lett., 31,* 3003, (1990).

K.B. Sharpless, R. Hanson, and S.Y. Ko, Catalytic Asymmetric Epoxidation, U.S. Patent 4,900,847, 1990 assigned to the Massachusetts Institute of Technology.

T. Shibata, D.G. Gilheany, B.K. Blackburn, and K.B. Sharpless, Ligand-Based Improvement of Enantioselectivity in the Catalytic Asymmetric Dihydroxylation of Dialkyl Substituted Olefins, *Tetrahedron Lett., 31,* 3817, (1990).

B. Moon Kim and K.B. Sharpless, A Short Route to β-Lactams: Use of Cyclic Sulfites From *Syn*-2,3-Dihydroxy Esters, *Tetrahedron Lett., 31,* 4317, (1990).

R.A. Johnson and K.B. Sharpless, Addition Reactions with Formation of Carbon-Oxygen Bonds: (ii) Asymmetric Methods of Epoxidation, "Comprehensive Organic Synthesis," Vol. 7, Barry M. Trost, Ed.; Pergamon Press, (1991), pp. 389-436.

S.S. Woodard, M.G. Finn, and K. Barry Sharpless, The Mechanism of Asymmetric Epoxidation. 1. Kinetics, *J. Am. Chem Soc., 113,* 106, (1991)

M.G. Finn and K.B. Sharpless, Mechanism of Asymmetric Epoxidation. 2. Catalyst Structure, *J. Am. Chem. Soc., 113,* 113, (1991).

P.R. Fleming and K.B. Sharpless, Selective Transformations of *threo*-2,3-Dihydroxy Esters., *J. Org. Chem., 56,* 2869, (1991).

R. Oi and K.B. Sharpless, Stereospecific Conversion of Chiral 1,2-Cyclic Sulfates to Chiral Imidazolines., *Tetrahedron Lett., 32,* 999, (1991).

C. Park, B. Moon Kim, and K.B. Sharpless, Catalytic Osmylation of Conjugated Dienes: A One-Pot Stereoselective Synthesis of Polyols., *Tetrahedron Lett.*, *32*, 1003, (1991).

B. McKee, D. Gilheany, and K.B. Sharpless, *R,R*-1,2-Diphenyl-1,2-ethanediol (stilbene diol)., *Org. Synth.*, *70*, 47, (1991).

K.B. Sharpless and I.E. Markó, Ligand-Accelerated Catalytic Asymmetric Dihydroxylation, U.S. Patent 4,965,364, 1990 assigned to Massachusetts Institute of Technology.

K.B. Sharpless, J.M. Klunder, and T. H. Onami, Optically Active Derivatives of Glycidol, U. S. Patent 4,946,974, 1990 assigned to Massachusetts Institute of Technology.

Y. Ogino, H. Chen, H.L. Kwong, and K.B. Sharpless, On the Timing of Hydrolysis/Reoxidation in the Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins Using Potassium Ferricyanide as the Reoxidant., *Tetrahedron Lett.*, *32*, 3965, (1991).

K.B. Sharpless, W. Amberg, M. Beller, H. Chen, J. Hartung, Y. Kawanami, D. Lübben, E. Manoury, Y. Ogino, T. Shibata, T. Ukita, New Ligands Double the Scope of the Catalytic Asymmetric Dihydroxylation of Olefins., *J. Org. Chem.*, *56*, 4585, (1991).

R. Oi and K.B. Sharpless, Facile Synthesis of Enantiopure *trans*-2,3-Diphenyl-1,4-Diazabicyclo[2.2.2.]Octane, *Tetrahedron Lett.*, *32*, 4853, (1991).

Y. Ogino, H. Chen, E. Manoury, T. Shibata, M. Beller, D. Lübben, and K.B. Sharpless, A Ligand Structure-Enantioselectivity Relationship for the Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins, *Tetrahedron Lett.*, *32*, 5761, (1991).

B. McKee, T. Kalantar, and K.B. Sharpless, Subtle Effects in the Asymmetric Epoxidation: Dependence of Kinetic Resolution Efficiency on the Monodentate Alkoxide Ligands of the Bystander Titanium Center, *J. Org. Chem.*, *56*, 6966 (1991).

R. Oi and K.B. Sharpless, Asymmetric Dihydroxylation of Acrolein Acetals: Synthesis of Stable Equivalents of Enantiopure Glyceraldehyde and Glycidaldehyde, *Tetrahedron Lett.*, *33*, 2095 (1992).

K.B. Sharpless, W. Amberg, Y. Bennani, G. Crispino, J. Hartung, K. Jeong, H. Kwong, K. Morikawa, Z.M. Wang, D. Xu, and X.L. Zhang, The Osmium-Catalyzed Asymmetric Dihydroxylation (AD): A New Ligand Class and a Process Improvement, *J. Org. Chem.*, *57*, 2768 (1992).

K.S. Jeong, P. Sjö, and K.B. Sharpless, Asymmetric Dihydroxylation of Enynes, *Tetrahedron Lett.*, *33*, 3833 (1992).

G. Crispino and K.B. Sharpless, Asymmetric Dihydroxylation of Squalene, *Tetrahedron Lett.*, *33*, 4273 (1992).

T. Kalantar and K.B. Sharpless, Transformations of Hydroxy Cyclic Sulfates: Stereospecific Conversion to 2,3,5-Trisubstituted Tetrahydrofurans, *Acta Chemica Scandinavica*, 47, 307 (1993).

L. Wang and K.B. Sharpless, Catalytic Asymmetric Dihydroxylation of Cis-Disubstituted Olefins, *J. Am. Chem. Soc.*, *114*, 7568 (1992).

D. Xu, G. A. Crispino, and K.B. Sharpless, Selective Asymmetric Dihydroxylation (AD) of Dienes, *J. Am. Chem. Soc.*, *114*, 7570 (1992).

T. Hashiyama, K. Morikawa, and K.B. Sharpless, α-Hydroxy Ketones in High Enantiomeric Purity from Asymmetric Dihydroxylation of Enol Ethers, *J. Org. Chem.*, *57*, 5067 (1992).

W. Amberg, Y.L. Bennani, R.J. Chadha, G.A. Crispino, W.D. Davis, J. Hartung, K.-S. Jeong, Y. Ogino, T. Shibata, and K.B. Sharpless, Syntheses and Crystal Structures of the Cinchona Alkaloid Derivatives used as Ligands in the Osmium-Catalyzed Asymmetric Dihydroxylation (AD) of Olefins, *J. Org. Chem.*, *58*, 844 (1993).

R.A. Johnson and K.B. Sharpless, Catalytic Asymmetric Epoxidation of Allylic Alcohols, "Catalytic Asymmetric Synthesis," Iwao Ojima, Ed.; VCH Publishers (1993).

R.A. Johnson and K.B. Sharpless, Catalytic Asymmetric Dihydroxylation, "Catalytic Asymmetric Synthesis," Iwao Ojima, Ed.; VCH Publishers (1993).

Z.M. Wang, X.L. Zhang, K.B. Sharpless, S.C. Sinha, A. Sinha-Bagchi, and E. Keinan, A General Approach to γ-Lactones via Osmium-Catalyzed Asymmetric Dihydroxylation. Synthesis of (–)- and (+)-Muricatacin, *Tetrahedron Lett.*, *33*, 6407 (1992).

E. Keinan, S.C. Sinha, A. Sinha-Bagchi, Z.M. Wang, X.L. Zhang, and K.B. Sharpless, Synthesis of All Four Isomers of Disparlure Using Osmium-Catalyzed Asymmetric Dihydroxylation, *Tetrahedron Lett.*, *33*, 6411 (1992).

H.C. Kolb and K.B. Sharpless, A Simplified Procedure for the Stereospecific Transformation of 1,2-Diols into Epoxides, *Tetrahedron*, *48*, 10515 (1992).

G.A. Crispino, P.T. Ho, and K.B. Sharpless, Selective Perhydroxylation of Squalene: Taming the Arithmetic Demon, *Science*, *259*, 64 (1993).

G.A. Crispino and K.B. Sharpless, Enantioselective Synthesis of Both Enantiomers of 7,7-Dimethyl-6,8-dioxabicyclo-[3.2.1]octane *via* Regioselective Asymmetric Dihydroxylation, *Synlett*, *1*, 47 (1993) .

H.C. Kolb, Y.L. Bennani, and K.B. Sharpless, Short and Practical Syntheses of (*R*)-(–)-Carnitine and (*R*)-(–)-γ-Amino-β-hydroxybutyric Acid (GABOB), *Tetrahedron: Asymmetry*, *4*, 133 (1993).

D. Xu and K.B. Sharpless, A Simple Route to Enantiomerically Enriched Oxazolidin-2-ones, *Tetrahedron Lett.*, *34*, 951 (1993).

Y.L. Bennani and K.B. Sharpless, Asymmetric Dihydroxylation (AD) of *N,N*-Dialkyl and *N*-Methoxy-*N*-methyl α,β-and β,γ-Unsaturated Amides, *Tetrahedron Lett.*, *34*, 2079 (1993).

Y.L. Bennani and K.B. Sharpless, Asymmetric Synthesis of γ-Hydroxy α,β-Unsaturated Amides via an AD-Elimination Process; Synthesis of (+)-Coriolic Acid, *Tetrahedron Lett.*, *34*, 2083 (1993).

Z.M. Wang, X.L. Zhang, and K.B. Sharpless, Asymmetric Dihydroxylation of Aryl Allyl Ethers, *Tetrahedron Lett.*, *34*, 2267 (1993).

S. Okamoto, K. Tani, F. Sato, K.B. Sharpless, and D. Zargarian, Synthesis of Optically Active Secondary Allylic Alcohols from Allylsilanes via Successive Asymmetric Dihydroxylation (AD) and Peterson Olefination Reactions, *Tetrahedron Lett.*, *34*, 2509 (1993).

G. Crispino, K.S. Jeong, H. Kolb, Z.M. Wang, D. Xu, and K.B. Sharpless, Improved Enantioselectivity in Asymmetric Dihydroxylations of Terminal Olefins Using Pyrimidine Ligands, *J. Org. Chem.*, *58*, 1958 (1993).

T. Göbel and K.B. Sharpless, Temperature Effects in Asymmetric Dihydroxylation: Evidence for a Stepwise Mechanism, *Angew. Chem., Int. Ed. Engl.*, *32*, 1329 (1993).

P.G. Andersson and K.B. Sharpless, A Dramatic Ligand Effect on the Relative Reactivities of Substituted Alkenes with Osmium Tetroxide, *J. Am. Chem. Soc.*, *115*, 7047 (1993).

M.S. VanNieuwenhze and K.B. Sharpless, Kinetic Resolution of Racemic Olefins via Asymmetric Dihydroxylation, *J. Am Chem. Soc.*, *115*, 7864 (1993).

Z.M. Wang and K.B. Sharpless, Asymmetric Dihydroxylation of α-Substituted Styrene Derivatives, *Synlett*, *8*, 603 (1993).

P.J. Walsh and K.B. Sharpless, Asymmetric Dihydroxylation (AD) of α,β-Unsaturated Ketones, *Synlett*, *8*, 605 (1993).

G.A. Crispino and K.B. Sharpless, Enantioselective Synthesis of Juvenile Hormone III in Three Steps from Methyl Farnesoate, *Synthesis*, *8*, 777 (1993).

D.V. McGrath, G.D. Brabson, K.B. Sharpless, and L. Andrews, Reinvestigation of the Infrared Spectra of Oxoosmium (VI) Esters by Isotopic Labeling, *Inorganic Chemistry*, *32*, 4164 (1993).

P.J. Walsh, Y.L. Bennani, and K.B. Sharpless, Asymmetric Dihydroxylation (AD)/Cyclization of *N*-DiBoc Allylic and Homoallylic Amines: Selective Differentiation of the Hydroxyl Groups, *Tetrahedron Lett.*, *34*, 5545 (1993)

K. Morikawa, J. Park, P.G. Andersson, T. Hashiyama, and K.B. Sharpless, Catalytic Asymmetric Dihydroxylation of Tetrasubstituted Olefins, *J. Am. Chem. Soc.*, 115, 8463 (1993).

K. Morikawa and K.B. Sharpless, Double Diastereoselection in Asymmetric Dihydroxylation, *Tetrahedron Lett.*, *34*, 5575 (1993).

M. Arrington, Y.L. Bennani, T. Göbel, P. Walsh, S.-H. Zhao, and K.B. Sharpless, Modified Cinchona Alkaloid Ligands Improved Selectivities in the Osmium Tetroxide Catalyzed Asymmetric Dihydroxylation (AD) of Terminal Olefins, *Tetrahedron Lett.*, *34*, 7375 (1993).

R. Oi and K.B. Sharpless, 3-(1*S*,2-Dihydroxyethyl)-1,5-Dihydro-3*H*-2,4-Benzodioxepine, *Org. Synth.*, in press.

Z.-M. Wang and K.B. Sharpless, Asymmetric Dihydroxylation of Tertiary Allylic Alcohols, *Tetrahedron Lett.*, in press.

Norrby, P-O, Kolb, H., and K.B. Sharpless, Calculations on the Reaction of Ruthenium Tetroxide with Olefins Using Density Functional Theory (DFT). Implications for the Possibility of Intermediates in the Osmium-catalyzed Asymmetric Dihydroxylation (AD), *Organometallics*, in press.

G. Crispino, A. Makita, Z.-M. Wang, and K.B. Sharpless, A Comparison of Ligands Proposed for the Asymmetric Dihydroxylation, *Tetrahedron Lett.*, in press.

H.C. Kolb, P.G. Andersson, Y.L. Bennani, G.A. Crispino, K.-S. Jeong, H.-L. Kwong, and K.B. Sharpless, On "The Origin of High Enantioselectivity in the Dihydroxylation of Olefins Using Osmium Tetroxide and Cinchona Alkaloid Catalysts", *J Am. Chem. Soc.*, in press.

I. Henderson, K.B. Sharpless, and C.-H. Wong, Synthesis of Carbohydrates via Tandem Use of the Osmium-Catalyzed Asymmetric Dihydroxylation and Enzyme-Catalyzed Aldol Addition Reactions, *J. Am. Chem. Soc.*, in press.

M.S. VanNieuwenhze and K.B. Sharpless, The Asymmetric Dihydroxylation of *cis*-Allylic Alcohols and Homoallylic Alcohols, *Tetrahedron Lett.*, in press.

H.C. Kolb, P.G. Andersson, and K.B. Sharpless, Towards an Understanding of the High Enantioselectivity in the Osmium Catalyzed Asymmetric Dihydroxylation (AD). Part 1: Kinetics, *J. Am. Chem. Soc.* in press.

ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

January 5, 1995

Mr. Peter Sobek
Strehlgasse 11
Vienna 19
Austria

Dear Peter:

You must have realized how sorry Isabel and I were during our last several visits to Vienna that we were never able to get together with you.

We plan to be back in Vienna from the 25th to the 28th of June, as I have been invited to give two lectures at the Josef Loschmidt Symposium. Needless to say, we would love to get together with you.

I wonder whether you have seen the article on Franz's old home in the December issue of House Beautiful. In any case, I enclose a copy.

My autobiography entitled Adventures of a Chemist Collector will be out in April, published by another Viennese, Weidenfeld. Of course, I have written a good deal about Franz.

All good wishes for the new year.

Sincerely,

Enclosure

By Appointment Only
ASTOR HOTEL SUITE 622
924 EAST JUNEAU AVENUE
MILWAUKEE WISCONSIN USA 53202
TEL 414 277-0730   FAX 414 277-0709

House Beautiful
Dec. '94

Biedermeier villa

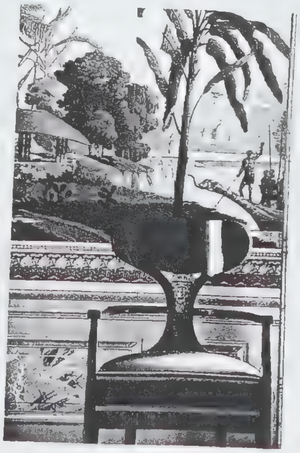
From a new book on Central European style: an early-19th-century Viennese summer house authentically restored

Built for an Austrian banker in the early 19th century, the Geymüllerschlössel has been restored and recently redecorated to its original Biedermeier splendor. ABOVE: One of the formal salons is wallpapered in a scenic Zuber pattern that reproduces an 1806 design called Hindustan. The sofa, armchairs, and side chairs—made of ebonized wood and ornamented with bronze paste lozenges, reliefs, and swan-shaped arms—were made in Vienna by the Danhauser Mobelfabrik in 1815; silk upholstery was redone after what was believed to be the original covering. In the corner, an 1820 Viennese ceramic stove.

BY SUZANNE SLESIN

The Biedermeier style, born in Austria and Germany in the first decades of the 19th century, has long been an international symbol of unpretentious elegance. Furniture makers such as Danhauser of Vienna combined maple and cherry and other light-colored woods with understated black-lacquer ornamentation. Case pieces often featured architectural motifs; chairs were designed in pared-down shapes reminiscent of Adam and Directoire styles. The result was furniture that is solid and clean-lined.

Long before the word *Biedermeier* became associated with the furniture style, it was synonymous with an attitude that considered comfort and respectability the prime virtues of society. With the development of trade and industry in Central Europe in 19th century, a new bourgeoisie was establishing itself and exerting its influence in cultural and political



In the Geymüllerschlössel's main entrance hall (FAR LEFT), a neoclassical niche flanked by wall clocks holds an 1820 Viennese turquoise-blue ceramic stove. CENTER: The symmetrical summer house features Gothic Revival arches, columned veranda, and a copper roof topped with a gold-leaf demilune weathervane. NEAR LEFT: An 1815 Viennese solid and veneered mahogany Biedermeier side chair.

ADAPTED FROM *MITTEL EUROPA: REDISCOVERING THE STYLE AND DESIGN OF CENTRAL EUROPE*. COPYRIGHT © 1994 BY SUZANNE SLESIN, STAFFORD CLIFF, DANIEL ROZENSZTROCH, AND GILLES DE CHABANEIX. CLARKSON POTTER/PUBLISHERS.

circles. A typical commission of this new elite is the house now known as the Geymüllerschlössel, which was built at the beginning of the 19th century as a summer house for Johann Jakob Geymüller, a Viennese banker. The architect was inspired by the garden follies of the time, and he incorporated Gothic and Arabic elements into the design of the eccentric building.

After a century of splendor, the house fell into decay, but in 1945 Franz Sobek bought the property and restored the house and its gardens. He also filled the rooms with his collections of Viennese clocks and fine Empire and Biedermeier pieces, donating the house to the Republic of Austria in 1965.

Recently, under the direction of Christian Witt-Dörring, curator at the Austrian Museum of Applied Arts in Vienna, the rooms have been redecorated and the furniture reupholstered to re-create the atmosphere of a Biedermeier house. ■

Architectural moldings, an uncarpeted parquetry floor, and a soft gray paint color lend a lightness to the anteroom on the second floor (RIGHT). The suite of stained pearwood and ormolu seating upholstered in emerald silk was made around 1805 for the Empress Maria Ludovica, second wife of the Emperor Franz. A gilt-bronze clock rests on a round French table from 1820. On either side of the settee are gilt-bronze torchères on pedestals that are Viennese, 1820. Flower pictures are actually porcelain plaques.

The yellow drawing room (BELOW) contains a suite of mahogany furniture made in Vienna by Danhauser in 1825. The clocks are part of a collection of 160 Viennese timepieces that date from the 1770s to the 1870s. Sofa is flanked by gilt-bronze torchères. The unusual swagged and tasseled upholstery, a reproduction of the original design, was specially woven in Florence. The carpet is a mid-19th-century French Aubusson.

On the back terrace (ABOVE), Gothic arches frame views of Geymüllerschlössel's small garden. The Gothic theme is echoed in cast-iron railing. White garden table is surrounded by painted pierced-metal chairs. A sarcophagus and garden ornament line the edge of the inlaid-stone floor.

For more details, see Reader Information

Department of
Chemistry & Biochemistry

Phone 219/631-7058
Fax 219/631-6652

University of Notre Dame
Notre Dame, Indiana 46556

June 6, 1994

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, WI 53211

Dear Alfred:

I was delighted to hear from you via the note you sent, along with the letter to Mr. Roach. Mr. Roach is a unique gentleman, owner of ABS and I am trying to help him achieve his goals for the Company.

I follow the same routine I have been following since I retired from Upjohn: Monday and Tuesday I am at Notre Dame in South Bend. Wednesday, Thursday and Friday I am in my office at Upjohn. I live at 3420 Pinegrove Lane, Kalamazoo, Michigan 49008.

Notre Dame phone: 219-631-7796
Upjohn phone: 616-385-7109

I keep fairly busy, but always have time for old friends.

It would be nice to get together.

With my best regards to your charming wife,

Jacob

J. Szmuszkovicz
Professor

JS:dkb

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

July 25, 1994

Professor Jacob Szmuszkovicz
Department of Chemistry & Biochemistry
University of Notre Dame
Notre Dame, Indiana 46556

Dear Jacob:

A long trip to Europe has delayed my thanking you for your happy note of June 6th.

Isabel and I drive to Indiana at least once a year, and when next we drive that way we will try to time our trip to be at Notre Dame on a Monday or Tuesday to be able to visit with you.

Fond regards to you and Rachel.

As always,

ALDRICH ®
Chemists Helping Chemists in Research and Industry

aldrich chemical company, inc.

Dr. Alfred Bader
Chairman

August 23, 1989

Prof. Robert G. Silberman
Department of Chemistry
State University College at Cortland
P.O. Box 2000
Cortland, New York 13045

Dear Prof. Silberman:

Thank you for your kind letter of August 17th.

Of course I understand your budget limitations and am sorry that I will not be able to be with you.

All good wishes.

Sincerely,

Alfred Bader

AB:mmh

P.O. Box 355, Milwaukee, Wisconsin 53201 USA, Telephone (414) 273-3850, Cable Aldrichem TWX 910-262-3052, Telex 26-843, FAX 414-273-4979

bcc: J. Nagarkatti, A. Griesinger

Dr. Alfred Bader
Chairman

February 11, 1988

Mr. N. A. Stylianides
81-5 Drexelbrook Drive
Drexel Hill, Pennsylvania 19026

Dear Mr. Stylianides:

Your interesting letter of February 2nd reminded me of our meeting in Philadelphia.

We do sell a number of research products to Greece, but the sales have not been substantial. It has not been our policy to give one company exclusive representation.

I am particularly interested in your saying that you and your father might set up a company in Greece to manufacture fine organic chemicals. If so, we would very much like to become your customer. However, we have found it very much better to buy from companies those compounds which they know how to produce, rather than to burden them with lists of compounds for which we are looking. These lists usually comprise compounds that we find difficult to make ourselves or difficult to purchase, and it would be far better for you to offer us what you know how to make.

As you probably know, the world's largest chemical exhibition is held every three years at the ACHEMA in Frankfurt, and the next ACHEMA will be there this coming June. We will have a stand, and our Managers from Aldrich Chemie in Germany will be there the entire week. Isabel and I plan to attend on the last day.

If your father would like to meet our people and discuss collaboration, that would be a very good time.

All good wishes, and best personal regards.

Sincerely,

Alfred Bader
AB:mmh

SIGMA-ALDRICH

P.O. Box 355 Milwaukee Wisconsin 53201 USA Telephone (414) 273-3850 Cable Aldrichem TWX 910-262-3052 Telex 26-843