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ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

October 22, 1993

Dr. Orrie M. Friedman
Chairman
Collaborative Research Inc.
100 Beaver Street
Waltham, Massachusetts 02154

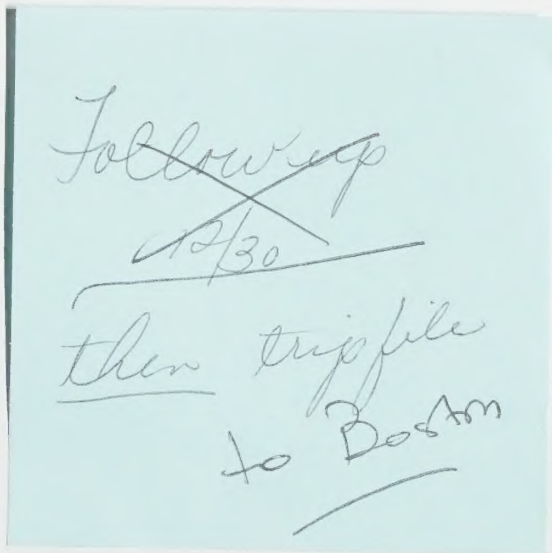
Dear Orrie:

It was so good to see you last week. Now I have to thank you for that most interesting package on Collaborative Research. As I am just leaving on two long trips from which I will not return until December 26th, I will study the package upon my return.

I visit the Boston area once or twice each year, and the next time I hope to have a chance to visit with you at Collaborative Research.

Best wishes.

Sincerely,



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Collaborative Research Incorporated

Annual Report 1992

Collaborative Research — The Year in Brief:

Fiscal 1992 was an exciting year of transition for Collaborative Research, Inc. During the past year, the Company:

- Nearly doubled revenues from continuing businesses, while substantially decreasing the operating loss.
- Maintained a strong cash position and ended the year with $7,100,000.
- Began investing to broaden the services of Collaborative Diagnostics by acquiring the Cytogenetics Laboratory of the Eunice Kennedy Shriver Center for Mental Retardation, Inc. and adding a flow cytometry laboratory.
- Built the infrastructure for and expanded the testing capabilities of Collaborative Diagnostics by hiring key management and technical staff.
- Secured a new facility to consolidate the operations of Collaborative Diagnostics and relocate the corporate offices of Collaborative Research.
- Received five new contracts and grants to bring the total money awarded within the past two years to more than $11 million in multi-year awards.
- Made significant progress on our existing contracts and grants.
- Initiated discussions with major pharmaceutical companies to explore commercial opportunities for leveraging our gene discovery and sequencing capabilities in the area of new drug discovery.

Financial Highlights

The following two tables show the growth in Collaborative's continuing businesses over the past three years:

To Our Shareholders:

Collaborative Research, Inc. is today involved in two primary businesses– research that will lead to new drug discovery evolving from the detection of disease-causing genes and the diagnosis of diseases having a genetic cause. The two aspects of our business are quite complimentary. While the discovery of new genes – which is the objective of much of the research taking place in our contracts and grants business – will lead to new therapeutics, the immediate application is in diagnostics, where the discovery of new genes can rapidly be put to use. It is relatively straightforward to detect the genes using synthetic DNA probes.

During fiscal 1992, Collaborative Research made significant progress in developing and growing these businesses. We began investing in the expansion of Collaborative Diagnostics, continued to secure substantial new government contracts and grants and began to focus our attention on leveraging the extensive research and technical capabilities of our contracts and grants business toward new drug discovery.

We also achieved a significant improvement in the financial results of our ongoing operations. Revenues from the Company's continuing businesses nearly doubled for this past year, compared to the previous year, while interest income and royalties also grew and the operating loss declined. We maintained a strong cash position and completed the year with $7.1 million and minimal debt. We do, however, expect to use our resources to continue expanding the diagnostic testing business.

In the pages following this letter, we have provided you with a detailed description of the Company's businesses and their accomplishments over the past year. I would like to take this opportunity to highlight a few of those accomplishments and, more importantly, to provide you with an overview of our plans and prospects for the future.

Contracts and Grants

We are proud of the continued success of our scientists in securing new government contracts and grants for projects associated with the Human Genome Initiative. During the past year, we were awarded five new contracts and grants – including several multi-year awards – which total more than $2 million. These bring the total of contracts and grants awarded within the past two years to more than $11 million, making Collaborative Research, Inc. one of the leading commercial human genome research firms in the U.S.

The new contracts and grants involve developing new or improved genetic tests or techniques, improving the technology for discovering disease genes or localizing the genes for specific genetic disorders. Our work on these projects keeps our technical staff at the cutting edge of research and technological developments related to gene mapping and sequencing. Our scientists have made substantial strides in accomplishing the objectives of the specific existing awards and have achieved a very favorable success rate in securing new awards in an increasingly competitive environment.

The Potential for New Drug Discovery

The activities in our contracts and grants business have significantly expanded our experience and expertise in all aspects of DNA sequencing and gene discovery. Finding the gene or genes responsible for a genetic disease opens the door to many powerful medical technologies which include: extremely precise diagnostic tools to establish the presence of or predisposition to a specific disease; DNA therapies to disable or replace a defective gene; new drug discovery and design; and procedures to predict toxicity reactions from conventional drug therapies.

Collaborative Research is well positioned to take advantage of these substantial commercial opportunities. We commercialize these advances immediately by developing and offering new diagnostic tests through Collaborative Diagnostics. At the same time, the Company is actively pursuing research that will lead to patentable drug discovery through its efforts directed at cloning the relevant genes for major human disorders, including tuberculosis, leprosy, non-insulin dependent diabetes, medullary thyroid carcinoma, facioscapulohumeral muscular dystrophy, bipolar affective disorder, asthma, hypertension, schizophrenia and prostate cancer. The research is being carried out under contract arrangements under which patents relating to gene discovery would be the property of Collaborative Research, Inc.

The Company continues exploration with a number of pharmaceutical corporations and others to secure the funding needed to mount a large-scale effort of discovering the genes responsible for diseases with a genetic component, such as cancer, as well as for those responsible for other specific major diseases.

Collaborative Diagnostics

Major steps were taken in the past year to strengthen and grow the Company's promising diagnostics business – Collaborative Diagnostics – into the country's preeminent, full-service genetic testing laboratory. With the acquisition of the Cytogenetics Laboratory of the Eunice Kennedy Shriver Center for Mental Retardation early in the year, we invested substantially in this business in order to meet the needs of our expanding customer base.

Collaborative Diagnostics focuses essentially on two markets – oncology and major genetic diseases. Throughout the year, we added new tests, new testing capabilities and new services to meet the needs of the physicians, genetic counselors, hospitals and laboratories who see patients requiring the kinds of specialized tests we perform. By becoming a full-service genetic testing laboratory, we have been able to secure a number of significant new accounts, including major hospitals and clinical laboratories that have agreed to refer all of their genetic tests to us for processing. A number of other major new arrangements of this nature are currently pending.

The growth of this business is attributable in large measure to the quality of our medical and technical staff and consultants and our strong research orientation. In this regard, we are most fortunate to have recently added to our staff Raymond G. Fenwick, Jr., Ph.D., who joined us as Vice President of Laboratory Operations for Collaborative Diagnostics. A nationally recognized authority in the field of DNA testing, Dr. Fenwick has twenty years of teaching, research and diagnostic laboratory management experience. Most recently, Dr. Fenwick served as Associate Professor and Director of the DNA Diagnostic Laboratory for the Institute for Molecular Genetics, Baylor College of Medicine, which is generally believed to be the leading DNA-based university testing laboratory in the country. He is responsible for laboratory operations and new test development for Collaborative Diagnostics and will be a driving force in the continued growth of this business.

Financial Results

The Company reported significantly improved results from operations for fiscal 1992, compared to fiscal 1991. Excluding revenues from the Biomedical Products Division, which was sold at the end of fiscal 1991, revenues from continuing businesses nearly doubled compared to the prior year, while the operating loss declined substantially. However, including revenues from the now discontinued Biomedical Products business, total revenues declined for the year.

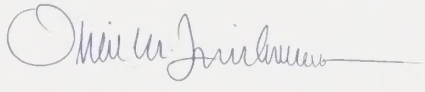
Robust growth in both the contracts and grants and diagnostic testing businesses contributed to the substantial increase in operating revenues. Interest income increased due to the increase in invested funds, resulting from the proceeds of the Biomedical Products Division sale. The increase in royalties reflects the commencement of royalty payments from The Dow Chemical Company for the sales by Dow's licensee, Pfizer, Inc., of recombinant chymosin (rennin), which is used to produce cheese. Collaborative developed this product under contract with Dow in the early 1980s.

Costs associated with the Company's continuing businesses increased in absolute dollars, while decreasing as a percent of sales throughout the year, reflecting the increased volume for these operations. Total costs and expenses declined, resulting primarily from the elimination of the fixed costs and expenses associated with the divested Biomedical Products business.

The Company's loss from operations declined substantially for the year, compared to last fiscal year. The net loss increased slightly for the year to $.19 per share, compared to $.16 per share for fiscal 1991. The 1991 net loss reflected a non-recurring gain of $2,104,000 (approximately $.20 per share) attributable to the sale of the Biomedical Products Division.

We are challenged and enthusiastic as we look toward the future. Our talented staff, state-of-the-art technical capabilities and complimentary businesses support a unique blend of short-term and long-term opportunities that can be leveraged for substantial future growth. Our immediate challenges are to leverage and transition our DNA technology from research to commercial applications, to secure new sources of financing to pursue new drug discovery and continue to grow Collaborative Diagnostics. In our effort to achieve these objectives, we have begun an active search for an outstanding Chief Executive Officer for Collaborative Research, Inc. As always, we are also indebted to you, our shareholders, for your continued interest and support.

Sincerely,



Orrie M. Friedman
Chairman and Chief Executive Officer

Contracts and Grants

Collaborative Research is one of the leading commercial human genome research firms in the United States. We are currently the recipient of thirteen separate contracts and grants that deal with various aspects of the Human Genome Initiative, and have been credited with a number of fundamental breakthroughs in genetic mapping and sequencing. In the past two years, we have received more than $11 million in government contracts and grants, primarily from the Genome Initiative.

Collaborative is one of only five large-scale DNA sequencing laboratories in the United States. Although other for-profit companies are carrying out work related to the Human Genome Initiative, we believe that Collaborative – with more than fifty full-time scientists working on genome research and extensive scientific capabilities – is the one best positioned to engineer rapid, broad-scale advances in the field.

New Contracts and Grants Awarded

Collaborative Research scientists continued their impressive record during the past year in securing new contracts and grants in an increasingly competitive and uncertain federal funding environment. Following are brief descriptions of the new contracts and grants awarded since our last report to you:

Phase II SBIR Grant to Develop Identity Testing Using PCR: Collaborative was awarded a Phase II SBIR grant to develop a DNA identification system using PCR (polymerase chain reaction) technology. The two-year, $500,000 award from the National Institute of General Medical Sciences began on March 1, 1992. A PCR-based DNA identification system would be a significant improvement over currently available methods for DNA typing. This system would not only be simple to perform, but would also require less DNA, reduce the time and expense of each typing analysis and allow analysis of degraded samples. These advantages would expand the application of DNA typing into areas where it is presently not cost-effective.

DOE Grant to Facilitate Genomic Sequencing and Disease Gene Discovery: The Company was also awarded a three-year, $945,000 grant by the Department of Energy (DOE) to improve one of the key technologies being utilized by scientists engaged in the Human Genome Initiative. The goal of the grant, which began March 15, 1992, is to improve the technology that enables scientists to clone and easily manipulate very large fragments of DNA by creating yeast artificial chromosomes (YACs). These long, contiguous pieces of DNA can be very useful in the short term for cloning disease genes. Such a discovery leads to the development of diagnostic tests and new therapies. This technology has great relevance to the Company's interests in DNA-based diagnostics and new drug discovery.

Phase II SBIR Contract to Develop a Test to Detect a Gene Implicated in Drug Compatibility and Cancer Susceptibility: Collaborative was awarded a Phase II SBIR contract to develop a DNA probe test for the prediction of the debrisoquine metabolism phenotype. The two-year, $500,000 award from the National Cancer Institute (NCI) began September 1, 1992.

The objective of the current contract is to develop a PCR -based DNA test that would be able to diagnose the status and form of this gene in greater than 98% of the population. The test currently available is able to ascertain the gene's status in only 95% of the population. Determining the status of this gene is important for two critical reasons: to determine if individuals with different forms of the gene are at a greater risk of developing certain forms of lung and bladder cancers, as suggested by current evidence; and to permit the prediction of an individual's compatibility with and metabolism rate for more than twenty commonly used drugs. Once developed, the test will be offered by Collaborative Diagnostics, the Company's diagnostic division reference laboratory, which already offers a wide range of DNA testing services to oncologists.

NIMH Genotyping Contract for Manic Depression: The Company was awarded a contract from the National Institute of Mental Health to assist NIMH Intramural Investigators find the chromosomal location(s) for the gene(s) responsible for bipolar affective disorder, which is commonly referred to as manic depression. The contract, worth $219,000 for the six-month period beginning September 30, 1992, can be renewed at the government's option for four successive twelve-month periods. Determining the chromosomal location of a gene is the first step in cloning that gene. Identification of the genes responsible for bipolar affective disorder should assist in the development of better diagnostics and therapeutics for this disease, which currently afflicts more than 3 million Americans.

VA Medical Center Contract to Establish Cell Lines for Schizophrenia: Collaborative was also awarded a contract by the Brockton/West Roxbury Veterans Affairs Medical Center to establish permanent cell lines from individuals in families with several cases of schizophrenia. These people are the subjects in a Department of Veterans Affairs Cooperative Studies program entitled, "A Genetic Linkage Study of Schizophrenia"

This September 1992 contract, the first to be awarded for this study, will provide an unlimited supply of DNA that will be used to determine the chromosomal location of the gene(s) responsible for schizophrenia, which afflicts approximately 2.5 million Americans. This localization is the first step in cloning the responsible gene(s) and will, in turn, also permit the development of better diagnostics and therapeutics for this disease.

Our progress on these and our existing grants help to ensure that Collaborative Research scientists remain on the leading edge of technological developments in the field of genetic mapping and sequencing and new drug discovery.

SUMMARY OF PRESENT CONTRACTS AND GRANTS

NATIONAL CENTER FOR HUMAN GENOME RESEARCH

- Develop "Framework" Maps for Human Chromosomes 10 and 20
- Construct a Physical Map for Human Chromosome 10
- Determine the Capability of Computer-assisted Multiplex Sequencing

NATIONAL CANCER INSTITUTE

- Clone the Gene Responsible for Medullary Thyroid Carcinoma
- Develop a DNA Test to Detect a Gene Implicated in Drug Compatibility and Cancer Susceptibility

NATIONAL INSTITUTE OF MENTAL HEALTH

- Map the Gene(s) Responsible for Bipolar Affective Disorder

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

- Sub-clone DNA Fragments and Prepare DNA for Automated Sequencing

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

- Convert VNTR Loci into PCR-based Probes and Develop a Population Database

MUSCULAR DYSTROPHY ASSOCIATION

- Clone the Gene Responsible for Facioscapulohumeral Muscular Dystrophy

WORLD HEALTH ORGANIZATION (two separate awards)

- Determine the Feasibility of Sequencing the Genomes of Leprosy and Tuberculosis

DEPARTMENT OF ENERGY

- Construct Chimera-free, High Copy Number YAC Libraries

VA MEDICAL CENTER

- Establish Permanent Cell Lines for Individuals in Families with Schizophrenia

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DISEASES BEING TARGETED IN PRESENT GENETIC RESEARCH AT [illegible]

Short-term Research	**Incidence**
• Tuberculosis	• 1.7 billion victims worldwide
• Non-insulin dependent diabetes	• 12 million living in U.S.
• Medullary thyroid carcinoma	• 15,000 living victims in U.S.
• Facioscapulohumeral muscular dystrophy (orphan drug status)	• 12,500 living victims in U.S.
Long-term Research	
• Bipolar affective disorder (Manic depression)	• 3 million affected in U.S.
• Schizophrenia	• 2.5 million living victims in U.S.
• Male patterned baldness	• 20 million affected in U.S.
• Hypertension	• 58 million sufferers
• Insulin dependent diabetes	• 500,000 living victims in U.S.
• Asthma	• 10 million sufferers in U.S.

Collaborative Diagnostics

Collaborative Diagnostics continues to be at the forefront of genetic research. Multiple, high-level disciplines and a broad spectrum of technologies give us an advantage among specialty laboratories providing comprehensive diagnostic services for diseases caused by genetic mutations.

From Collaborative's core specialties of molecular genetics and human genome research, Collaborative Diagnostics has expanded its technological capabilities to include biochemistry, flow cytometry and, through the Company's acquisition from the Shriver Center of its Cytogenetics Laboratory, full-scale cytogenetics.

By steadily expanding the number of tests and types of services available to our client base, Collaborative Diagnostics continues to build on its core businesses in both inherited mutations (genetic disease) and acquired mutations (cancer). Collaborative Diagnostics provides a broad range of diagnostic information and counseling relevant to specific diseases. For cancer, this means information provided by molecular oncology, flow cytometry and cancer cytogenetics, and for inherited disease, it means information provided by molecular genetics, cytogenetics and biochemistry.

Oncology Services

Since the early 1970s, tremendous advancements have been made in the understanding of the biology of cancer. Today, virtually all research in this area is guided by the knowledge that cancer is a genetic disease, in that cells within a tumor inherit malignant characteristics from a transformed parent cell.

Collaborative Diagnostics utilizes a battery of sophisticated techniques to aid in diagnosing and monitoring cancer. For example, DNA probes can identify genetic rearrangements useful in the diagnosis and follow-up of leukemias and lymphomas. Flow cytometry had become a standard cell sorting tool in the diagnosis of certain leukemias and lymphomas. Cytogenetic analysis facilitates the identification of chromosomal abnormalities found in various cancers.

Collaborative Diagnostics combines these methodologies to provide physicians with the most comprehensive information presently available in order to help direct critical treatment decisions.

Inherited Diseases

Collaborative Diagnostics performs conclusive tests for a number of inherited diseases, including a diagnostic test for cystic fibrosis, which was developed using the Company's technology. The continual collaboration between researchers and diagnosticians is a fundamental distinction of Collaborative Diagnostics.

Among the other services offered are tests for fragile X syndrome, the most common inherited form of mental retardation, adult polycystic kidney disease, chromosome analysis of amniotic fluid and chorionic villus sampling (CVS) and maternal serum alpha-fetoprotein (AFP) screening. The laboratory has completed more than 15,000 amniotic fluid analyses and 20,000 AFP analyses and was the first in Greater Boston to offer CVS analysis. In the effort to provide complete service, we have added molecular, biochemistry and cytogenetic laboratories and now offer professional genetic counseling services.

Parents at risk for having children with genetic abnormalities need sensitive, informed counseling at the pre-conception, post-conception or post-partum stages. Our commitment to complete service includes qualified genetic counseling. We work with the physician and family to clarify risks and options.

Operations and Administrative Improvements

We took substantial strides during fiscal 1992 to build the infrastructure and strengthen the operational and administrative capabilities of Collaborative Diagnostics to support our expanding business. During the past year, the Company:

- hired the management, sales and technical staff required to support a full-service diagnostic laboratory;
- added critical new technological capabilities, including cytogenetics and flow cytometry;
- consolidated all aspects of our diagnostic laboratory operations into one location;
- obtained the necessary licenses to operate in every state in the U.S.;
- improved customer services, including the establishment of a local courier service and an automated lab tracking system for sample record-keeping and reporting; and
- centralized our new test development group to ensure the rapid development and transfer of tests to the laboratory.

These improvements will enable us to maximize the potential of and rapidly expand our business in the coming year.

Collaborative Diagnostics - An Overview

Technology Utilized:

- Molecular Genetics
- Cytogenetics
- Biochemical Genetics
- Flow Cytometry

Laboratory Accreditations:

- Clinical Laboratory Improvement Amendments (CLIA)
- Massachusetts Department of Health
- Medicare
- New York State Department of Health

Proficiency Testing Programs:

- College of American Pathologists
- American Association of Blood Banks
- Foundation for Blood Research
- New York State Department of Health

Partial List of Tests Offered

Oncology:

- Gene Rearrangement Analysis
- Leukemia/Lymphoma Immunophenotyping
- Bone Marrow Transplant Monitoring
- Leukemia Cytogenetics

Genetics:

- Fragile X Syndrome
- Cystic Fibrosis
- Adult Polycystic Kidney Disease
- Y Chromosome Detection and Analysis
- Parentage Testing
- Amniotic Fluid Chromosome Analysis
- Chorionic Villus Sample Analysis
- Maternal Serum Alpha-fetoprotein

Financials

Management's Discussion and Analysis of Financial Condition and Results of Operations

Overview

Financial Condition

Results of Operations

Costs and Expenses

Total costs and expenses decreased substantially by 41% to $7.6 million in fiscal 1992 from $12.9 million in fiscal 1991 due mostly to the sale of the Biomedical Products business. Total costs and expenses for fiscal 1990 were $12.6 million

Costs of product and service revenue decreased approximately $3.1 million from $4.2 million in fiscal 1991 to $1.1 million in fiscal 1992 reflecting the reduction of approximately $3.6 million of product cost associated with the Biomedical Products business. That reduction was offset by approximately a $.5 million

Consolidated Statements of Operations

For the Years Ended August 31, 1992, 1991 and 1990	1992	1991	1990
Revenues:			
Biomedical Product Revenue (Note 2)	$ -0-	$ 6,412,078	$ 6,347,74[illegible]
Product & Service Revenue (Note [illegible])	[illegible]	[illegible]	[illegible]
Research Contract Revenue (Note 1)	4,210,053	2,193,245	2,139,5[illegible]
Royalties (Note 1)	121,34[illegible]	[illegible]	[illegible]
Interest Income	[illegible]	[illegible]	[illegible]
Total [illegible]	[illegible]	[illegible]	[illegible]
Costs and Expenses:			
Cost of Product & Service Revenue	1,132,[illegible]	[illegible]	[illegible]
Cost of Research Contract R[illegible]	[illegible]	[illegible]	[illegible]
Research and [illegible]	[illegible]	[illegible]	[illegible]
Selling, General and Administrative	2,493,305	4,265,266	4,[illegible]
Total Costs and Expenses	7,587,04[illegible]	[illegible]	[illegible]
Operating L[illegible]	[illegible]	[illegible]	[illegible]
Non-recurring Gains (Notes 2 and [illegible])	[illegible]	[illegible]	[illegible]
Net Loss	$ (2,078,711)	$ (1,6[illegible])	[illegible]
Net Loss per Common Share (Note 1)	$ (.1[illegible])	[illegible]	[illegible]
Weighted Average Common Shares Outstanding	10,662,551	[illegible]	[illegible]

[illegible]

[illegible] million in 1991 reflecting the increase in [illegible] with that business and its marginal con[illegible] tract revenue were $2.0 million.

Company-funded research and development expenses decreased substantially, approximately $2.0 million from $2.3 million in fiscal 1991 to $.3 million in fiscal 19[illegible] [illegible] were, in prior years, subsidized by the Company. The substantial decrease was offset by a slight increase in process development [illegible] diagnostic testing business. Research [illegible]

[illegible]

Gain on Sale of Biomedical Products Business

[illegible] Company [illegible] Biomedical Products business to Becton Dickinson and Company [illegible] up to a maximum of $1.6 million over the next five years. Th[illegible] by $.5 million of expenses pertaining to the transaction leaving [illegible] net gain of $2.1 million which reduced the net loss for the [illegible]

Gain from Settlement of Sandoz Contract

During fiscal 1990, the Company reached a settlement with Sandoz AG regarding the development contract for pro[illegible] nase which resulted in a non-recurring gain of $655,000 and [illegible]

Consolidated Balance Sheets

August 31, 1992 and 1991	1992	1991
Assets:		
Current Assets		
Cash and Cash Equivalents (Note 1)	$ 7,144,140	$ 8,080,918
Short-term Investments (Note 1)	-0-	360,000
Receivables:		
Trade, and Other (less allowance for doubtful accounts of $74,000 in 1992 and $16,000 in 1991)	389,066	846,325
Inventories (Note 1)	268,040	341,049
Prepaid Expenses	65,251	221,564
Total Current Assets	7,766,497	9,849,856
Equipment and Leasehold Improvements, at Cost (Notes 1 and 6)		
Laboratory and Scientific Equipment	675,505	679,478
Leasehold Improvements	1,363,803	1,285,537
Office Equipment and Furniture	468,444	457,202
Furnished Plant and Equipment	148,663	105,000
	2,656,415	2,527,217
Less Accumulated Depreciation and Amortization	1,872,977	1,387,650
	784,438	1,139,567
Goodwill (net of accumulated amortization of $38,580) (Note 6)	803,678	-0-
Total Assets	$ 9,354,613	$ 10,989,423
Liabilities and Shareholders' Equity:		
Current Liabilities:		
Accounts Payable	$ 402,007	$ 507,517
Accrued Expenses (Note 3)	785,833	1,073,869
Short-term Note Payable (Note 8)	265,500	-0-
Deferred Contract Revenue	343,817	118,637
Current Maturities of Capital Lease Obligations (Note 6)	148,037	-0-
Total Current Liabilities	1,945,194	1,700,023
Deferred Compensation (Note 7)	162,537	111,388
Capital Lease Obligations, Net of Current Maturities (Note 6)	275,136	-0-
Commitments and Contingencies (Note 5)		
Shareholders' Equity (Notes 1 and 7):		
Common Stock, $.10 Par Value - Authorized 17,500,000 shares; Issued and Outstanding — 10,664,166 shares in 1992 and 10,661,541 shares in 1991	1,066,416	1,066,154
Series B Restricted Stock, $.10 Par Value - Issued and Outstanding — 57,512 shares in 1992 and 1991	5,751	5,751
Additional Paid-in Capital	37,122,427	37,123,140
Accumulated Deficit	(31,198,854)	(29,120,143)
Instalment Receivable from Sale of Series B Restricted Stock	(76,966)	(97,030)
Total Shareholders' Equity	6,915,774	9,077,872
Total Liabilities and Shareholders' Equity	$ 9,354,613	$ 10,790,253

The accompanying notes are an integral part of these consolidated financial statements

Consolidated Statements of Cash Flows

For the Years Ended August 31 [illegible] and [illegible]	[illegible]	[illegible]	[illegible]
Cash Flows from Operating Activities:			
Net Loss	$ (2,078,711)	$ (1,687,095)	$ (2,627,263
Adjustments to Reconcile Net Loss to Net			
Cash Used by Operating Activiti			
Gain on Sale of Net Assets	(12,217)	(2,104,000)	-0-
Gain on Contract Settlement	-0-	-0-	(515,4
Depreciation and Amortization	212,321	1,460,979	1,755,022
Loss on Sale of Equipment	-0-	-0-	25,321
Deferred Compensation	44,387	18,313	29,7
Provisions for Accounts Receivabl			
ind Inventory Reserves	69,801	176,345	141,419
Changes in Assets and Liabiliti			
(Increase) Decrease in Current Assets			
Short-term Investments	360,000	75,000	(75,00
R vables	(138,633)	(316,779)	(15
Inventor	-0-		
Prepaid Expens			
Increase (Decrease) in Current			
Accounts P			
Bank Overdraft	-0-		
Accrued Expenses			
Deferred Contract Revenue			
Tot			
Net Cash Used by Operating Activit			
Cash Flows from Investing Activit			
Purchase of Equipment and Leasehold Improvements	(167,319)	(229,51	
Proceeds from Sale of Net Assets	969,000	8,100,000	-0
Payments for Net Assets Acquired			
Net Cash Provided by (Used for) Investing Activities	313,196	7,870,482	(15
Cash Flows from Financing Activitie			
Proceeds from Sale of Stock	6,305	780	50
Principal Payments under Capital Lease Obligations	(30,026)	(39,219)	(3
Net Cash Used by Financing Activities	(23,721)	(38,439)	(2
Net Increase (Decrease) in Cash and Cash Equivalents	(1,536,773)	5,563,651	(1,087,713)
Cash and Cash Equivalents at Beginning of Year	8,680,913	3,117,262	4,204,975
Cash and Cash Equivalents at End of Year	$ 7,144,140	$ 8,680,913	$ 3,117,262

[illegible]

Consolidated Statements of Shareholders' Equity

	Common Stock	
Three Years Ended August 31, 1990, 1991 and 1992	Shares	Amount
Balance at August 31, 1989	10,655,141	$1,065,514
Exercise of Stock Options	2,500	250
Cancellation / Termination of Stock Options		
Net Loss		
Balance at August 31, 1990	10,657,641	1,065,764
Exercise of Stock Options	3,900	390
Cancellation / Termination of Stock Options		
Net Loss		
Balance at August 31, 1991	10,661,541	1,066,154
Exercise of Stock Options	1,128	113
Cancellation / Termination of Stock Options		
Net Loss		
Balance at August 31, 1992	10,662,669	$1,066,267

The accompanying notes are an integral part of these Consolidated Statements.

Notes to Consolidated Financial Statements

1. Summary of Significant Accounting Policies

Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its subsidiaries. All material intercompany balances and transactions have been eliminated.

Research and Development Contract Accounting

The Company participates in fixed-price and cost-plus fixed-fee contracts. Certain contracts have no stated deliverables associated with them. The Company is, however, required to prepare a scientific report for the Company's research and development expenses under cost-plus and fixed-price contracts are recognized in the proportion that costs incurred bear to total estimated costs. At the Company's option, the payments for amounts billed by these contracts and the fee is charged to operations. Unbilled costs represent costs and expenditures on contracts plus earned fees thereon, over billings.

Cash Equivalents and Short-term Investments

Cash equivalents and short-term investments consisting of certificates of deposit, money market funds and U.S. Government and agency obligations with maturities of three months or less when purchased are stated at cost, which approximates market value. As of August 31, 1992, the Company had unrealized gains of $15,000.

Statement of Cash Flows

For purposes of the statement of cash flows, the Company considers all highly liquid investments with a maturity of three months or less when purchased to be cash equivalents. Interest and income taxes paid amounted to $1,000 for the three years ended August 31, 1992. During the year ended August 31, 1992, a capital lease obligation of $453,169 was incurred when the Company entered into a lease agreement for new office and laboratory equipment. For the year ended August 31, 1990, a capital lease obligation of $[illegible] was incurred when the Company entered into a lease agreement for new equipment. That lease obligation was transferred to Becton Dickinson on August 30, 1991. (See Note 2.)

Equipment and Leasehold Improvements

Equipment and leasehold improvements are depreciated over their estimated useful lives using the straight-line method. The estimated useful life for leasehold improvements is the initial term of the lease plus an extension option period. Equipment and other depreciable assets' useful lives vary from three to five years. Expenditures for maintenance and repairs are expensed as incurred.

Series B Restricted Stock Shares	Series B Restricted Stock Amount	Additional Paid-in Capital	Accumulated Deficit	Installment Receivable from Sale of Stock (Note 2)	Total Shareholders' Equity
57,512	$5,751	$36,906,294	$(31,805,785)	$(2,000,000)	$3,108,860
		17,063			17,063
		(8,222)			(8,222)
			(262,263)		(262,263)
57,512	5,751	36,915,135	(32,068,048)	(2,000,000)	2,852,838
		2,340			2,340
		107,684			107,684
			(1,087,169)		(1,087,169)
57,512	5,751	37,025,159	(33,155,217)	(2,000,000)	1,875,693
		6,042			6,042
		(6,761)			(6,761)
			(2,078,731)		(2,078,731)
57,512	$5,751	$37,024,440	$(35,233,948)	$(2,000,000)	$(203,757)

Service Revenue

Revenues are recognized in the period in which services are rendered. Revenues subject to Medicare or third party reimbursement are recorded at estimated reimbursement amounts.

Royalty Revenue

Royalty revenues are recorded as earned. Royalties represent receipts from The Dow Chemical Company and CIBA Corning for license agreements for renin and PSMA, respectively.

Net Loss per Common Share

Net loss per common share has been computed based upon the weighted average number of common shares outstanding during each period. Common share equivalents consisting of outstanding stock options have not been used to compute the loss per common share as the effect would be antidilutive.

Reclassifications

Certain amounts previously reported in the consolidated financial statements have been reclassified to conform with the 1992 presentation. Such reclassifications have not affected previously reported results.

2. Gain on Sale of Biomedical Products Business

On August 31, 1992, the Company sold the net assets of its Biomedical Products business to Boston Electronics and Corporation for $10 million, plus a potential earnout of the next four years. The transaction resulted in a non-recurring, pre-tax gain of $3.7 million (after $0.8 million of related expenses), resulting in a net gain of $2.1 million (or $.04 per share) in fiscal 1993.

3. Gain from Settlement of Sandoz Contract

In fiscal 1993, the Company reached a settlement with Sandoz AG on a contract which was terminated on August 31, 1992. The settlement resulted in a gain of $650,000.

4. Income Taxes

At August 31, 1993, the Company has available federal net operating loss carryforwards, subject to Internal Revenue Service review, of approximately $42,267,000 to offset against future taxable income, expiring at various dates through 2007. In addition, the Company had investment tax credits and research and experimentation credits of approximately $1,150,000 available to offset future federal income tax liabilities, expiring at various dates through 2001.

The Financial Accounting Standards Board has issued pronouncements that would require the Company to change its method of accounting for income taxes beginning no later than fiscal 1993. Because the Company has significant net operating loss carryforwards, implementation of the pronouncements is not expected to have a material effect on the Company's reported financial position and results of operations.

5. **Commitments and Contingencies:**

At August 31, 1992 the Company has operating leases for office space and laboratory facilities which require minimum lease payments during each of the following years:

1993	$ 313,287
1994	313,287
1995	313,287
1996	47,000
1997	47,000
	$ 1,033,863

Rental expense charged to operations was approximately $193,000 in 1992, $218,000 in 1991 and $210,000 in 1990, including operating expenses.

There is an interference proceeding pending in the United States Patent and Trademark Office and corresponding proceedings in the European Patent Office and in the United Kingdom, with regard to patent matters pertaining to certain expanding upon the outcome, the Company has rights to certain patent rights in the United Kingdom and in Europe as well as in the United States may be adversely affected. Management is presently unable to predict the likely outcome of these proceedings, but believes that these proceedings will not have a material adverse effect on the consolidated financial statements as of August 31, 1992.

6. **Capital Lease Obligations:**

The Company leases certain office and laboratory equipment under capital lease agreements. The net book value of the equipment was approximately $[illegible] at August 31, 1992. Future minimum lease payments under the capital leases together with the present value of the net minimum lease payments at August 31, 1992, are as follows:

1993	$ 177,822
1994	177,822
1995	119,471
Total minimum lease payments	475,115
Less: Amount representing interest	43,972
Present value of total minimum lease payments	431,143
Less: Current portion	268,007
	$ 163,136

7. **Shareholders' Equity:**

Series B Restricted Stock

On January 21, 1985 the shareholders approved an amendment to the Restated Articles of Organization of the Company designating 625,000 shares of common stock as Series B Restricted Stock ("Series B Stock") and adopting a Series B Restricted Stock Purchase Plan (the "Plan"). The Plan terminated August 31, 1986, and 57,512 shares remain outstanding. In the event of liquidation, holders of common stock are entitled to receive, prior to and in preference to any distribution of the Company's assets to the holders of Series B Stock, the amount of $0.5500 per share, or [illegible] (10) times the amount which, after such distribution, would remain available for distribution to holders of the Series B Stock. After such preferential distribution, the remaining assets, if any, of the Company would be distributed ratably to the holders of common stock and Series B Stock.

Common Stock Options

The Company has [illegible] option plans and agreements [illegible] below.

The Company adopted an incentive stock option plan (the "[illegible] Plan") in October 1981, pursuant to which 250,000 shares were reserved for issuance to key employees. No further options may be granted under the 1981 Plan. In August 1983, the Company adopted a [illegible] plan, as amended in October 1984 (the "1984 Plan"), pursuant to which 500,000 shares of common stock were reserved for issuance to key employees. In May 1988, the number of reserved shares was reduced to 300,000. No further options may be granted under the 1981 Plan.

In 1984, the Company adopted the 1984 Stock Option Plan (the "1984 Plan"), pursuant to which 500,000 shares were reserved for issuance to key employees and consultants. The options may be granted at prices not less than 50% of the fair market [illegible] of the common stock [illegible] granted.

In 1988, the Company adopted a stock option plan (the "1988 Plan") [illegible] 500,000 shares were reserved for issuance to key employees and consultants. The options may be granted at prices not less than 50% of the fair market value of the common stock on the date of grant. [illegible] separate agreements ("Other Stock Option Agreements"), the Company has granted directors and certain consultants of the Company options to purchase common stock.

In 1991, the Company adopted a stock option plan (the "1991 Plan"), under which 500,000 shares were reserved for issuance

to key employees and consultants. No incentive stock option may be granted with a per share exercise price less than the fair market value per share at the date of grant. Non-incentive stock options may be granted at such price as may be determined by the Stock Option Committee, but not less than the par value of the common stock.

Fair market value is determined by computing the average value per share between the closing bid and asked price on the date of grant. The Company accounts for the compensation arising from the grant of stock options under certain plans as follows: a) at the date of grant, the Company establishes both a prepaid asset and a deferred compensation liability for the difference between the option price and fair market value; b) the Company amortizes the prepaid compensation to expense over the vesting period of the related options; and c) on the date of exercise, the Company removes the deferred compensation liability from its balance sheet and credits the appropriate equity accounts. For presentation purposes, the prepaid compensation is netted against the deferred compensation and the net amount is reflected as a deferred compensation liability on the balance sheet.

The compensation expense charged to operations was approximately $46,000, $18,000 and $3,000 during 1992, 1991 and 1990, respectively. Deferred compensation to be charged to future operations in the year in which these options become exercisable will be approximately $50,000, $47,000, $47,000 and $12,000 for 1993, 1994, 1995 and 1996, respectively.

The remaining outstanding options become exercisable through August 1996. There were 876,750 common shares available for future grants at August 31, 1992 under existing stock option plans. Plan data are summarized as follows:

	1992	1991	1990
Option shares:			
Granted	323,000	367,875	567,000
Exercised	(3,625)	(3,937)	(2,500)
Cancelled	(107,225)	(135,424)	(139,875)
Outstanding August 31	1,117,814	914,064	877,125
Price range of outstanding options at end of period	$.20-$11.94	$.20-$11.94	$.20-$11.94
Price range of exercised options during period	$.88-$1.38	$.20	$.20

8. Accrued Expenses:

The components of accrued expenses at the respective dates are as follows:

August 31,	1992	1991
Payroll and related expenses	$ 170,955	$ 232,765
Vacation accrual	110,188	74,478
Professional fees	38,559	221,538
Severance	25,000	120,000
Facilities relocation	79,039	112,703
Equipment lease accrual	131,610	-0-
All other	230,484	309,795
	$ 785,835	$1,070,879

9. Acquisition:

On September 30, 1991, the Company acquired the Prenatal Diagnostic Laboratory of the Eunice Kennedy Shriver Center for Mental Retardation, Inc., located in Waltham, Massachusetts, for a final purchase price of $.9 million consisting of $.2 million in cash and a note payable of $.7 million. The note payable, which is non-interest bearing, matures in the first quarter of fiscal 1993. The acquisition has been accounted for as a purchase. The purchase price was allocated to the net assets acquired, equipment and furniture based on their estimated fair market value, which was approximately $90,000. The remainder of the purchase price was allocated to goodwill which is being amortized over twenty years.

10. Incentive Savings Plan (401K):

The Collaborative Research Incentive Savings Plan (the "Plan") is maintained for the benefit of its employees. The Plan became effective March 1, 1985 and allows employees with one full year of service to make certain tax deferred voluntary contributions which the Company matches at the rate of 50% for the first 2% of salary and 25% for the next 4% of salary, limited to the first $50,000 of annual salary. On November 4, 1986, the Company granted to each active employee one hundred (100) shares, or a pro-rated amount, of non-certificated stock. Vesting occurred immediately for those employees with ten (10) or more years of service, and all others on March 4, 1987. The Company contributed $[illegible], $34,500 and $31,852 to the Plan for 1992, 1991 and 1990, respectively.

11. Executive Bonus Plan:

In fiscal 1990, the Company adopted an Executive Bonus Plan pursuant to which certain executives may receive a bonus equal to varying percentages of their respective base salaries depending upon the Company's adjusted cash flow for the fiscal year. No amounts related to the Plan were charged to operations in 1992, 1991 and 1990.

Report of Independent Public Accountants

To the [illegible] Collaborative Research, Inc.:

We have audited the accompanying consolidated balance sheets of COLLABORATIVE RESEARCH, INC. (a Massachusetts corporation) and subsidiaries as of August 31, 1992 and 1991, and the related consolidated statements [illegible] August 31, 1992. These financial statements are the responsibility of the Company's [illegible] an opinion on these [illegible].

[illegible]

[illegible]

Arthur Andersen & Co.

[illegible]

Range of Stock Prices

The Company's common stock is traded on the NASDAQ National Market System (ticker symbol "CRIC"). This table sets [illegible] quotations for each fiscal quarter [illegible] 1991 as furnished by the National Association of Securities Dealers [illegible].

Common Stock Prices

	1992		1991	
	High	Low	High	Low
First Quarter	[illegible]	[illegible]	[illegible]	[illegible]
Second Quarter	[illegible]	[illegible]	[illegible]	[illegible]
Third Quarter	[illegible]	[illegible]	[illegible]	[illegible]
Fourth Quarter	[illegible]	[illegible]	[illegible]	[illegible]

Selected Consolidated Financial Data

[illegible] August 31	1992	1991	1990	1989	1988
[illegible] Revenues	$ 792,225	[illegible]	[illegible]	[illegible]	[illegible]
Research Contract Revenue	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total Revenues	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Net Loss	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Per Share	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Average Common Shares	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total Working Capital	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total Assets	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Stockholders' Equity	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

Annual Meeting

The Annual Meeting of Shareholders will take place on Monday, January 25, 1993 at The First National Bank of Boston, 100 Federal Street, Boston, Massachusetts, at 1:00 p.m

SEC Form 10-K

Shareholders may obtain a copy of the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission, including the financial schedules, by sending a written request to:

Treasurer
Collaborative Research, Inc
[illegible]
Waltham, Massachusetts 02154

Independent Public Accountants
Arthur Andersen & Co.
One International Plac
Fort Hill Square
Boston, Massachusetts 02110

Collaborative Research, Inc.
Corporate Headquarters
[illegible]
Waltham, Massachusetts 0215[illegible]
617-487-7979
FAX: 617-487-7960

Questions concerning taxpayer identification numbers, transfer procedures and other stock or stockholder matters should be addressed to the Stock Transfer Agent at:

The First National Bank of Boston
Shareholders Services Division
Mail Stop: 45-02-09
P.O. Box 644
Boston, Massachusetts 02102-0644

Board of Directors

***#Orrie M. Friedman**
Chairman
Collaborative Research, Inc

#Mark D. Friedman
Attorney
Mitsui & Co. (U.S.A.), Inc

@*Lawrence Levy
Chairman & President
[illegible] Corporation

@Seymour Rothfeld
Private Investor

@#Paul C. Zamecnik
Principal Scientist
Worcester Foundation for
Experimental Biology

@Member of the Audit and Finance Committee
**Member of the Executive Committee*
#Member of the Stock Option Committee

Officers

Orrie M. Friedman
Chairman, Chief Executive Officer and President

William P. Johnson
[illegible]
Manager — Collaborative Diagnostics

Gerald F. Vovis
Senior Vice President — Research & Development

Fenel M. Eloi
Vice President — Finance, Treasurer
and Chief Financial Officer

David C. Chapin
[illegible]
Mr. Chapin is a Partner of Ropes & Gray

Collaborative Research Incorporated 100 Beaver Street, Waltham, Massachusetts 02154 (617)487-7979

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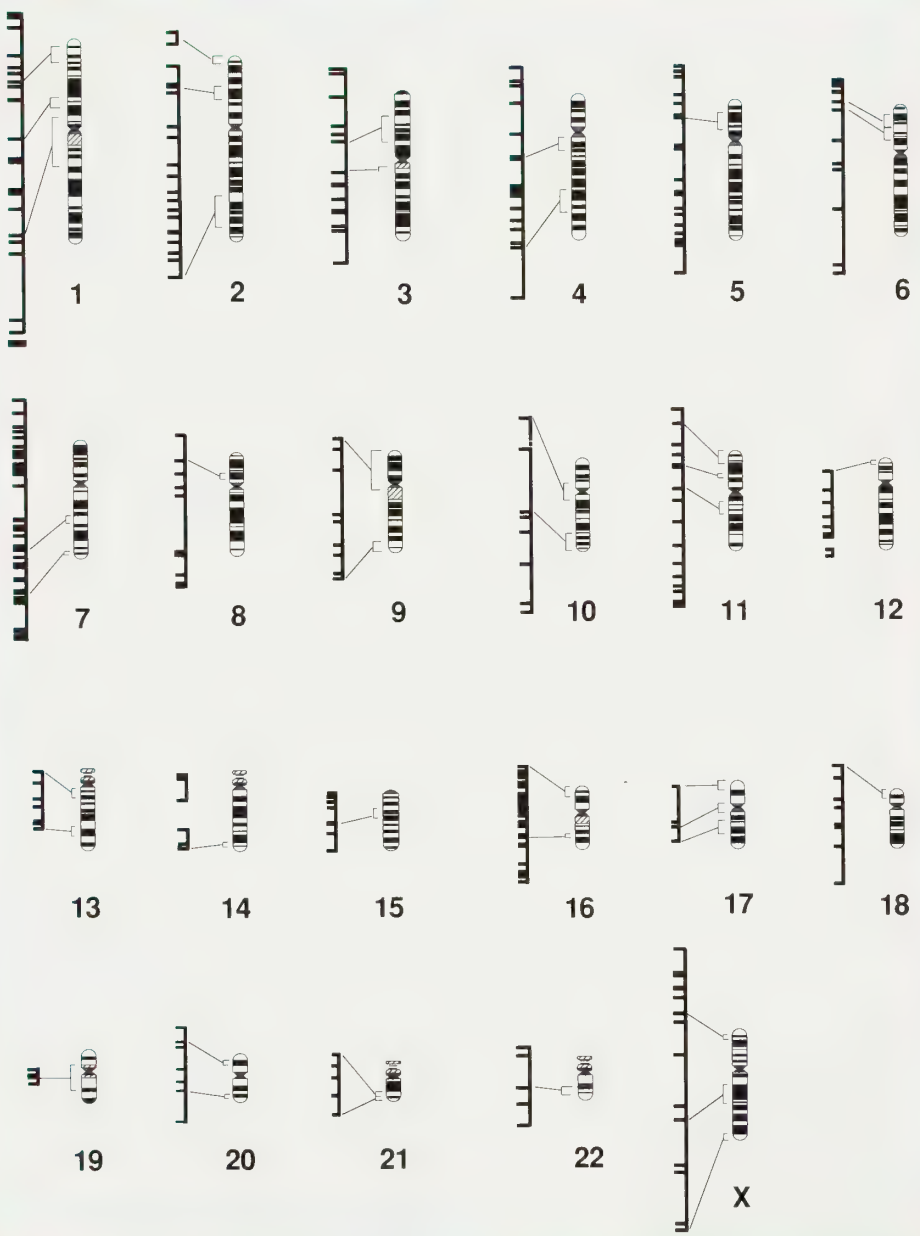
Volume 51 Number 2 October 23, 1987



RFLP Linkage Map of Entire Human Genome

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A Genetic Linkage Map of the Human Genome

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Summary

We report the construction of a linkage map of the human genome, based on the pattern of inheritance of 403 polymorphic loci, including 393 RFLPs, in a panel of DNAs from 21 three-generation families. By a combination of mathematical linkage analysis and physical localization of selected clones, it was possible to arrange these loci into linkage groups representing 23 human chromosomes. We estimate that the linkage map is detectably linked to at least 95% of the DNA in the human genome.

Introduction

The extensive genetic variation present in humans represents an invaluable resource for molecular biology and for medical investigation (McKusick, 1986). Cloning and characterization of genes underlying human inherited traits has helped elucidate the molecular basis for a wide range of physiological processes in higher organisms (e.g., Goldstein and Brown, 1983). The difficulty with extending this approach to all heritable traits and diseases is that the vast majority of such genes are known only by their phenotype: their protein product is unknown. In experimental higher organisms, the time-honored approach to the study and, more recently, the cloning of such genes is to identify their location in the genome through the use of a genetic linkage map.

The notion of a genetic map dates back to 1911, when Sturtevant, while an undergraduate in T. H. Morgan's lab, realized that linkage information could be used to determine the relative position of genes along a chromosome, and at once produced the first genetic map, comprising five sex-linked loci in Drosophila (Sturtevant, 1913, 1965). At the time, the internal consistency of the linear map provided important support for the chromosomal theory of inheritance. Over the next 75 years, complete genetic linkage maps proved to be essential tools for studying the properties of mutations. Genetic markers gained new importance with the advent of recombinant DNA, since cloned markers provide starting points for cloning closely linked genes by chromosomal walking (Bender et al., 1983). Unfortunately, the construction of complete genetic linkage maps has traditionally required the isolation of hundreds of single-gene mutations with easily scored phenotypes, followed by extensive interbreeding of mutant stocks to ascertain the map position of the mutations. Such an effort has only been practical in a few intensively studied genetic systems, such as Escherichia coli, Saccharomyces cerevisiae, Drosophila melanogaster, Caenorhabditis elegans, Zea mays, and Mus musculus. In humans, despite great interest and occasional successes in detecting linkage (e.g., Mohr, 1954), construction of a genetic map seemed impractical.

Several years ago, Botstein et al. (1980) argued that it was feasible to construct a complete linkage map of the human genome using common variations in DNA sequence, most conveniently visualized as restriction fragment length polymorphisms (RFLPs), as genetic markers. With such polymorphisms as markers, geneticists could study inheritance in existing pedigrees, since all individuals would be heterozygous at many loci.

Systematic screening has revealed that RFLPs are not uncommon (Willard et al., 1985) in the human genome, although the majority show only a low degree of polymorphism. Through the study of the inheritance of randomly selected RFLPs in human families, linkage has been detected to a number of human diseases, including Duchenne muscular dystrophy (Davies et al., 1983), Huntington's disease (Gusella et al., 1983), cystic fibrosis (Tsui et al., 1985; Knowlton et al., 1985; Wainwright et al., 1985; White et al., 1985b), adult polycystic kidney disease (Reeders et al., 1985), retinoblastoma (Cavenee et al., 1983), familial Alzheimer's disease (St George-Hyslop et al., 1987), bipolar affective disorder (Egeland et al., 1987), von Recklinghausen neurofibromatosis (Barker et al., 1987a; Seizinger et al., 1987), multiple endocrine neoplasia type 2a (Mathew et al., 1987; Simpson et al., 1987) and familial polyposis (Bodmer et al., 1987). The existence of nearby DNA probes has facilitated the molecular cloning of the genes for chronic granulomatous disease (Royer-Pokora et al., 1986), Duchenne muscular dystrophy (Monaco et al.,1986), and retinoblastoma (Friend et al., 1987; Lee et al., 1986).

The availability of a complete linkage map of the human genome would greatly amplify the power of this approach to human molecular genetics. With such a map, (1) the chromosomal location of newly discovered linkages would be known at once; (2) several nearby starting points would be available for efforts to clone disease genes; (3) prenatal or presymptomatic diagnosis of individuals at risk would become more accurate, through the use of markers flanking the disease gene, and more widely available,

since most families would likely be informative for at least some of the markers near the disease; (4) the search for disease genes would become more efficient, because a map would assure that the entire genome had been scanned and because multilocus analysis would decrease the number of meioses required to detect linkage (Lathrop et al., 1984; Lander and Botstein, 1986a,b); (5) it would become possible to map heterogeneous genetic disorders (Lander and Botstein, 1986a) and rare recessive diseases (Lander and Botstein, 1987), as well as to test whether there is a genetic basis for disorders whose inheritance is currently unclear; and (6) one could begin to study the nature of recombination in humans. In addition, the availability of a genetic map would assist efforts to construct a complete physical map of the human genome; islands of overlapping clones could be genetically ordered by means of polymorphisms they detect, even before the intervening DNA had been identified.

In view of the value of a complete human linkage map, an international collaboration called the Centre d'Etude du Polymorphisme Humain (CEPH) was organized in 1984. The CEPH maintains cell lines from 40 three-generation human families, consisting in most cases of four grandparents, two parents, and an average of eight children. Such families are ideal for genetic mapping, because the *cis–trans* relationship (i.e., linkage phase) of alleles in the parents can frequently be inferred from grandparental DNAs (Figure 1) and, once this is determined, crossovers can be counted in the meioses giving rise to the children. The CEPH distributes DNAs from these families to collaborating investigators around the world. Since collaborators use the same reference panel of families, data generated by one group can be used by others to detect new linkages. In particular, crossovers in the families can be mapped, allowing the order of probes to be determined. The collective efforts of the CEPH collaboration will eventually produce a far more detailed map than could any group alone. To date, hundreds of RFLPs have been identified (Willard et al., 1985; Schumm et al., 1987; Nakamura et al., 1987), including an increasing number with a higher degree of polymorphism, but relatively few have been mapped. At present, detailed RFLP linkage maps have been published only for the X chromosome (21 markers spanning 185 cM) (Drayna et al., 1984), a chromosomal region in 6p (four linked loci spanning 20 cM) (Leach et al., 1986), a chromosomal region in 13q (nine loci spanning 70 cM) (Leppert et al., 1986), and preliminary reports for chromosome 7 (Donis-Keller et al., 1986) and chromosome 12 (White et al., 1986).

We report the construction of a linkage map of the human genome, based on the pattern of inheritance of 403 polymorphic loci, including 393 RFLPs, in a panel of DNAs from 21 three-generation families. By a combination of mathematical linkage analysis and physical localization of selected clones, it was possible to arrange these loci into linkage groups representing the 23 human chromosomes. We estimate that the linkage map is detectably linked to at least 95% of the DNA in the human genome.

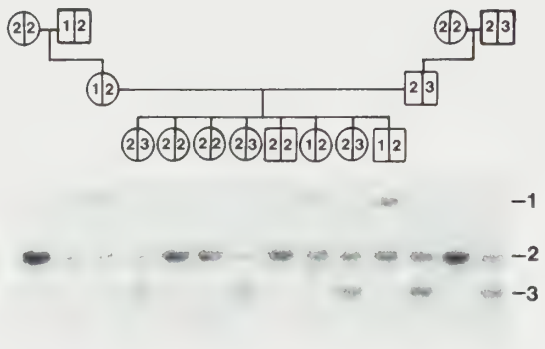


Figure 1. Inheritance of a RFLP Locus in a CEPH Family

RFLP probe CRI-L1265, which detects a single locus on chromosome 5, displays three alleles on Southern hybridization to DNA from CEPH reference family 1341 digested with the restriction endonuclease TaqI. The alleles correspond to single fragments of size 10.0 kb, 7.7 kb, and 6.5 kb, respectively. For each of the parents, one can infer which allele was inherited from the grandmother and which from the grandfather (i.e., linkage phase is known). For each child, one can then infer the grandparental origin of their two alleles.

Results and Discussion

Identification, Characterization and Pedigree Studies of RFLPs

We tested 1680 clones from a Charon 4A phage library of human genomic DNA (Lawn et al., 1978) to see whether they detected restriction fragment length polymorphism by hybridization to Southern blots of DNA from five unrelated individuals, each digested with six to nine restriction enzymes. Over 500 probes were identified that detected variable banding patterns indicative of polymorphism (Schumm et al., 1987). From this collection, a subset of the 180 probes detecting the highest degree of polymorphism were selected for inheritance studies in the 21 CEPH families for which cell lines were available or for which a sufficient quantity of DNA for these studies could be provided by the CEPH. An additional 46 probes detecting polymorphism were similarly identified from human genomic cosmid libraries (D. Bowden, unpublished results), from phage libraries of human genomic DNA grown on recombination deficient hosts (Wyman et al., 1986), and from two chromosome-specific phage libraries, described below. The probes were hybridized to Southern blots of DNAs from the parents of the families to confirm the observed polymorphic pattern and to determine which families were informative for linkage analysis (by virtue of one or both parents being heterozygous for the RFLP). For each informative family, genotypic data were then gathered on all family members. (Probes with fewer than 45 informative meioses in the families were omitted from further analysis.) Table 1 summarizes the probe–enzyme combinations for these markers, together with their heterozygosities, polymorphism information content (PIC; Botstein et al., 1980), and number of informative meioses in the CEPH families studied.

As part of a parallel effort to produce high-resolution linkage maps of chromosomes 7 and 16, inheritance data were similarly gathered for 42 probes on chromosome 7 (Barker et al., 1987) and for 37 probes on chromosome 16 (T. Keith, unpublished results) isolated from libraries enriched for these chromosomes; probes on these chromosomes also arose in the whole genome screen described above, yielding a total of 59 probes on chromosome 7 and 40 on chromosome 16. We also studied the inheritance of 54 further RFLPs detected by probes that had been isolated by other investigators and localized to chromosomes or subchromosomal regions (Table 2). In all, we determined the inheritance of 360 RFLPs. In addition, we included in our analysis previously published data on 46 loci that had been contributed to the CEPH (Table 3).

Construction of the Linkage Map

Multilocus genetic linkage analysis is required for the accurate construction of human linkage maps, including the determination of locus order. Such multilocus analysis has been limited until recently by the inability of available algorithms and computer programs to analyze more than three or four loci simultaneously (Leppert et al., 1986; Drayna et al., 1984; Morton et al., 1986; Smith, 1986). We recently developed faster algorithms, which permit simultaneous maximum likelihood map distance estimation in CEPH families for many loci (Lander and Green, 1987), and have embodied these algorithms in computer programs (Lander et al., 1987; Barker et al., 1987a). This has made possible the use of new analytical strategies for constructing the map.

Construction of Linkage Groups and Physical Assignment to Chromosomes

The traditional measure of support for linkage of a pair of loci, the LOD score, is defined as the $\log_{10}$ of the ratio of the probability that the data would have arisen if the loci are linked to the probability that the data would have arisen if the loci are unlinked (Morton, 1955). The conventional threshold for declaring linkage is a LOD score of 3.0, which would indicate that the observed data are 1000-fold more likely to have occurred for a pair of linked loci than for a pair of unlinked loci. However, since an arbitrary pair of loci is a priori 50-fold more likely to be unlinked than linked, a LOD score of 3.0 provides only about 20:1 odds in favor of linkage (Morton, 1955). In other words, one expects about one in 20 independent linkages with a LOD score of 3.0 to be spurious. Because of the large number of comparisons performed in the present study, we adopted a stricter threshold of LOD 4.0 in order to lower the odds of spurious linkage to about 200:1 against. (In fact, three spurious LOD scores of 4.0 between pairs of loci on separate chromosomes occurred in the data set. The anomalies became obvious upon multipoint analysis and were resolved by physical assignment of various linked loci.)

Throughout the course of the project, linkage data were analyzed on a weekly basis in order to monitor the overall progress toward a linkage map and to select a subset of the probes for physical assignment to chromosomes. We describe here only the final rounds of analysis, performed on the completed data set. The analysis began with the computation of the recombination fraction and LOD score between each of the 81,003 pairs of loci. Using the threshold of LOD 4.0 for linkage, the loci could be grouped into linkage groups and unlinked loci. Linkage groups were immediately assigned to specific chromosomes if they contained a probe whose chromosomal location had previously been determined. Otherwise, linkage groups were assigned to chromosomes by means of hybridizing one or more probes to panels of rodent–human hybrid cells containing varying human chromosomal complements. Unlinked probes were also assigned in this manner. Each autosome contained at least one linkage group. We then turned to multilocus analysis to detect linkage between syntenic linkage groups, to detect linkage between linkage groups and the unlinked probes, and to construct genetic maps for each chromosome.

Multilocus Analysis of Chromosome Maps

In constructing maps in experimental organisms, one can usually determine the correct order of the loci first (based on data from three-point crosses) and then estimate the map distances between consecutive loci. Individual three-point crosses are less efficient for analyzing human crosses, because different families are informative for different triplets of loci; integrating all of the information requires simultaneous multilocus analysis of the loci. To determine the genetic order of a set of loci, map distances and the corresponding likelihoods should ideally be determined for all possible orders of the loci (Ott, 1985); a genetic order is accepted if it is considerably more likely to have given rise to the data than alternative orders.

For linkage groups containing only six loci, it is straightforward to compute the maximum-likelihood multipoint map for each of the 360 possible orders for the loci and to then compare the likelihoods (Lander and Green, 1987; Lander et al., 1987). Of course, this becomes impossible as the number of loci increases, since the number of possible orders grows exponentially. Instead, maps can be constructed by sequentially adding loci to a map (as indeed is done in experimental genetic organisms). We have employed two such strategies for making maps of the more densely covered chromosomes, both of which led to the same results.

In the first approach, loci were first sorted by their informativeness, and a pair of highly informative linked loci were chosen as the nucleus of the map. The next most informative locus was then selected and placed in each possible position with respect to the two loci. The maximum likelihood distances for each of the orders were computed, and the locus was added to the map if one order was preferred over the others by a 100:1 odds ratio (i.e., if the observed data were 100-fold more likely to have arisen with that order than with any other order). If the locus could not be uniquely placed in this manner, another locus was tested in the same way. Thus, only conservative additions were made to the map. When no remaining lo-

Table 1. CRI RFLP Probes

Probe	Chr.	Enz.	Alleles	Het	PIC	Meioses	Assignment
CRI-C52	1	E	3	.57	.50	193	linkage
CRI-L56	1	M	2	.33	.26	105	linkage
CRI-L112	1	B	2	.45	.38	144	linkage
CRI-L336	1	R	7	.76	.71	260	hybrid panel
CRI-L423	1	M	2	.40	.33	139	linkage
CRI-L461	1	T	2	.50	.38	158	linkage
CRI-L501	1	T	>6	.50	.48	170	hybrid panel
CRI-L589	1	E	2	.52	.40	172	linkage
CRI-L673	1	M	2	.40	.29	127	linkage
CRI-L744	1	R	5	.52	.52	161	hybrid panel
CRI-L816	1	B	2	.24	.19	72	linkage*
CRI-L931	1	T	2	.26	.21	78	linkage
CRI-L943	1	T	2	.36	.33	120	linkage
CRI-L1039	1	M	2	.40	.31	94	linkage
CRI-L1046	1	T,M	16	.74	.74	262	linkage
CRI-L1054	1	M	4	.36	.33	122	linkage
CRI-L1191	1	M	2	.40	.33	128	linkage
CRI-L1199	1	M	8	.90	.88	283	hybrid panel
CRI-L1201	1	T	2	.43	.33	132	linkage
CRI-L1209	1	T	6	.64	.64	234	hybrid panel
CRI-L1226	1	M	5	.67	.62	210	linkage
CRI-R39	1	M	2	.17	.14	49	linkage
CRI-R117	1	M	2	.29	.26	91	linkage
CRI-R275	1	E	2	.26	.21	86	linkage
CRI-R629	1	H	2	.50	.33	158	linkage
CRI-R1002	1	T	2	.52	.38	169	linkage
CRI-S182	1	M	3	.43	.40	148	linkage
CRI-C13B	2	P	4	.67	.60	229	linkage
CRI-C36	2	E	2	.33	.29	122	linkage
CRI-C43	2	E	2	.21	.21	69	linkage
CRI-C84	2	E	2	.50	.38	160	linkage
CRI-L22	2	T	6	.79	.76	261	linkage
CRI-L34	2	M	3	.40	.31	146	linkage
CRI-L301	2	T	2	.48	.36	155	linkage
CRI-L379	2	M	2	.21	.21	63	linkage
CRI-L452	2	Bg	4	.55	.45	182	linkage
CRI-L523	2	R	2	.38	.26	120	linkage
CRI-L586	2	M	2	.40	.36	128	hybrid panel
CRI-L625	2	M,T	7	.62	.57	215	hybrid panel
CRI-L750	2	T	2	.26	.26	78	linkage
CRI-L1202	2	T	2	.26	.19	85	linkage
CRI-L1229	2	T	4	.57	.45	185	linkage
CRI-L1247	2	M	2	.55	.40	172	linkage
CRI-L1287	2	M	2	.21	.21	69	linkage
CRI-P20	2	Bg	2	.24	.21	82	linkage
CRI-P40	2	E	2	.50	.38	153	linkage
CRI-P166	2	M	4	.67	.62	217	linkage
CRI-R4	2	T	2	.48	.38	155	linkage
CRI-R40	2	Bg,M	5	.38	.36	128	linkage
CRI-R221	2	T	4	.40	.40	139	linkage
CRI-R322	2	Bg,T	5	.55	.40	185	linkage
CRI-C17	3	M	4	.69	.57	235	linkage
CRI-L162	3	T	2	.19	.17	61	linkage*
CRI-L182	3	M	2	.43	.36	131	linkage
CRI-L325	3	M	4	.40	.33	146	linkage
CRI-L619	3	T	6	.40	.36	140	linkage
CRI-L892	3	T	5	.71	.64	231	hybrid panel
CRI-L1169	3	M	3	.74	.69	260	linkage
CRI-P112	3	M	2	.40	.33	122	linkage
CRI-P145	3	T	2	.48	.36	134	hybrid panel
CRI-R59	3	M	5	.67	.52	245	linkage
CRI-R96	3	M	3	.64	.60	251	linkage
CRI-R208	3	Bg,M	5	.76	.71	258	hybrid panel
CRI-R532	3	M	5	.62	.48	191	linkage
CRI-U1	3	M	2	.36	.31	116	linkage
CRI-C47	4	B	2	.33	.26	101	linkage
CRI-C82	4	M	4	.52	.48	174	linkage
CRI-L9	4	H	2	.40	.29	116	linkage
CRI-L114	4	H	2	.29	.24	91	linkage
CRI-L231	4	M	2	.17	.17	64	linkage
CRI-L503	4	T	2	.48	.38	183	hybrid panel
CRI-L527	4	T	2	.45	.38	159	linkage
CRI-L1190	4	M,T	4	.67	.52	208	linkage
CRI-L1210	4	Bg	2	.29	.24	91	linkage
CRI-L1408	4	M	3	.50	.43	176	linkage
CRI-R107	4	M	2	.50	.38	162	linkage
CRI-R171	4	Bg	2	.31	.26	106	linkage
CRI-R227	4	E,T	6	.81	.76	267	linkage
CRI-R234	4	Bg	8	.57	.57	193	linkage
CRI-R622	4	T	4	.21	.21	70	linkage
CRI-V820	4	T	3	.67	.55	215	linkage
CRI-C44	5	M	6	.74	.67	238	linkage
CRI-C61	5	T	4	.64	.57	199	linkage
CRI-L45	5	M	4	.76	.74	250	linkage
CRI-L118	5	P	2	.29	.26	117	linkage
CRI-L123	5	M,R	>20	.71	.71	231	hybrid panel
CRI-L334	5	T	5	.64	.60	161	linkage
CRI-L372	5	M	4	.64	.57	224	hybrid panel
CRI-L401	5	T	2	.38	.33	118	linkage
CRI-L407	5	T	2	.50	.33	181	linkage
CRI-L433	5	M,P	6	.60	.50	192	linkage
CRI-L540	5	P	3	.52	.50	170	linkage
CRI-L986	5	T	2	.45	.33	143	linkage
CRI-L1072	5	T	2	.36	.31	113	linkage
CRI-L1155	5	T,Hc	4	.48	.36	164	linkage
CRI-L1194	5	M	2	.33	.29	103	linkage
CRI-L1200	5	T	3	.40	.36	120	linkage
CRI-L1265	5	T	4	.62	.57	209	linkage
CRI-P148	5	T	3	.57	.57	188	linkage
CRI-P152	5	Bg	2	.38	.29	113	linkage
CRI-R36	5	T	4	.57	.57	170	linkage
CRI-R379	5	M	4	.55	.55	147	linkage
CRI-R535	5	M	3	.45	.43	145	linkage
CRI-R1005	5	H	2	.19	.17	64	linkage
CRI-T39	5	M	2	.48	.33	103	linkage
CRI-V1022	5	M	4	.55	.48	186	linkage
CRI-L171	6	T,M	8	.55	.45	195	hybrid panel
CRI-L320	6	M,T	6	.50	.40	166	linkage
CRI-L322	6	M	3	.48	.43	144	linkage
CRI-L994	6	T	2	.31	.26	112	hybrid panel
CRI-L1065	6	R	11	.74	.74	243	hybrid panel
CRI-L1077	6	T	5	.50	.43	152	hybrid panel
CRI-P74	6	P	2	.36	.31	127	linkage
CRI-R125	6	H	2	.40	.33	122	linkage
CRI-R368	6	M	4	.52	.45	180	linkage
CRI-T18	6	R	3	.12	.07	48	linkage*
CRI-T22	6	H	10	.26	.26	85	linkage
CRI-L281	7	M,T	11	.79	.71	273	linkage
CRI-L390	7	Bg	2	.19	.17	60	linkage
CRI-L544	7	M	2	.52	.43	177	linkage
CRI-L751	7	M	3	.71	.57	249	linkage
CRI-L819	7	H	2	.40	.29	138	linkage
CRI-L887	7	M	3	.55	.48	195	linkage
CRI-L917	7	H,Hc	4	.71	.67	237	hybrid panel
CRI-L966	7	R	8	.74	.69	242	hybrid panel
CRI-L1020	7	H,T	8	.79	.76	271	hybrid panel
CRI-L1033	7	M	2	.36	.31	119	linkage
CRI-L1238	7	E	2	.50	.43	167	linkage
CRI-P137	7	T	2	.45	.40	142	linkage

Table 1. (continued)

Probe	Chr.	Enz.	Alleles	Het	PIC	Meioses	Assignment
CRI-R12	7	M	5	.31	.29	102	linkage
CRI-R40	7	M	2	.45	.36	143	linkage
CRI-R53	7	Bg	3	.40	.33	126	linkage
CRI-R944	7	M	4	.43	.36	141	linkage
CRI-R967	7	M	4	.40	.33	113	linkage
CRI-C96	8	Bg	4	.29	.24	88	linkage
CRI-L40	8	Bg	2	.40	.31	125	linkage
CRI-L186	8	T	4	.57	.55	176	linkage
CRI-L388	8	T	2	.40	.33	137	linkage
CRI-L413	8	P	5	.64	.60	218	hybrid panel
CRI-L580	8	T	2	.55	.45	174	linkage
CRI-L1212	8	M	2	.19	.17	58	linkage
CRI-L1251	8	M	4	.62	.48	207	hybrid panel
CRI-L1427	8	T	5	.40	.38	134	linkage
CRI-R150	8	H	2	.50	.31	137	hybrid panel
CRI-R191	8	M,T	7	.74	.64	253	linkage
CRI-R370	8	M	2	.50	.40	169	linkage
CRI-U4	8	M	3	.36	.33	99	linkage
CRI-V822	8	E	2	.57	.40	181	linkage*
CRI-V1225	8	E	4	.69	.69	200	linkage
CRI-L659	9	T	2	.45	.38	141	linkage
CRI-L1022	9	P	2	.26	.24	90	hybrid panel
CRI-L1263	9	T	4	.64	.52	225	hybrid panel
CRI-L1424	9	H	2	.43	.31	143	linkage*
CRI-P110	9	E	2	.45	.33	151	linkage
CRI-P111	9	T	2	.55	.36	169	linkage
CRI-R3	9	E	2	.50	.33	154	linkage
CRI-L368	10	H	9	.74	.74	232	hybrid panel
CRI-L647	10	T	5	.50	.48	152	hybrid panel
CRI-L893	10	E	2	.40	.31	136	linkage
CRI-L941	10	M	2	.36	.31	118	linkage
CRI-L1005	10	H	2	.31	.21	96	linkage
CRI-L1083	10	M	3	.55	.45	182	hybrid panel
CRI-L424	11	E,H	4	.57	.55	171	linkage
CRI-L451	11	E,M	4	.36	.31	102	linkage
CRI-L605	11	M	7	.71	.50	227	hybrid panel
CRI-L762	11	T	5	.62	.50	206	linkage
CRI-L834	11	M	2	.45	.33	142	linkage
CRI-L937	11	Hc	2	.33	.24	97	linkage
CRI-L944	11	T	5	.45	.36	149	linkage*
CRI-L962	11	M	6	.71	.62	245	hybrid panel
CRI-L1382	11	M,T	4	.57	.48	173	linkage
CRI-R83	11	H,M,T	6	.71	.69	265	linkage
CRI-R365	11	Bg	5	.48	.48	157	linkage
CRI-R397	11	R	4	.43	.38	157	linkage
CRI-R548	11	P	2	.21	.19	76	linkage
CRI-R975	11	T	2	.50	.38	159	linkage
CRI-V928	11	M	3	.48	.40	144	linkage
CRI-C2	12	P,E	8	.71	.69	229	linkage
CRI-C86	12	P	4	.17	.14	56	linkage
CRI-L303	12	M	2	.24	.21	82	linkage
CRI-L375	12	T	3	.57	.43	183	hybrid panel
CRI-L409	12	E,Hc	4	.60	.45	185	linkage
CRI-L416	12	E	10	.52	.50	167	hybrid panel
CRI-L809	12	M	3	.45	.40	155	hybrid panel
CRI-P102	12	M	2	.24	.24	68	linkage
CRI-P153	12	M	2	.45	.36	129	linkage
CRI-R102	12	T	4	.60	.52	203	linkage
CRI-V834	12	M	2	.50	.33	117	linkage
CRI-R214	13	T	2	.40	.31	131	linkage
CRI-V1134	13	H	3	.60	.52	188	linkage
CRI-C70	14	M	6	.71	.67	235	linkage
CRI-L329	14	T	3	.48	.36	114	linkage
CRI-L436	14	T	2	.52	.36	203	hybrid panel
CRI-L1013	14	Bg	2	.43	.33	152	linkage
CRI-L1113	14	P	2	.48	.33	159	linkage
CRI-L146	15	H,M	6	.62	.55	183	linkage
CRI-L389	15	Bg	6	.21	.21	84	hybrid panel
CRI-L442	15	M	3	.60	.50	193	linkage
CRI-L1204	15	M	2	.57	.43	167	hybrid panel
CRI-P78	15	B	2	.36	.33	121	linkage
CRI-P452	15	M	2	.24	.21	82	linkage
CRI-R382	15	M	4	.62	.60	191	linkage
CRI-L223	16	T	2	.48	.40	159	linkage
CRI-L922	16	H,Hc	4	.50	.43	163	linkage
CRI-R99	16	H,M	4	.64	.62	226	linkage
CRI-L581	17	T	3	.55	.50	196	hybrid panel
CRI-L946	17	M	3	.43	.40	132	linkage
CRI-P3	17	M	2	.52	.31	155	linkage
CRI-L84	18	M	2	.36	.31	119	linkage
CRI-L159	18	P	23	.74	.74	264	hybrid panel
CRI-L261	18	M	2	.52	.40	181	linkage
CRI-L821	18	M	2	.26	.26	81	linkage*
CRI-L1156	18	M	3	.57	.55	179	linkage
CRI-P30	18	Bg,T	4	.52	.43	161	linkage
CRI-R397	18	P	5	.57	.55	190	hybrid panel
CRI-L127	20	M	2	.43	.31	130	linkage
CRI-L355	20	Bg	22	.74	.74	257	hybrid panel
CRI-L1214	20	Bg	17	.98	.98	334	hybrid panel
CRI-L1239	20	M	2	.40	.33	115	linkage
CRI-L427	21	R	25	.95	.93	327	hybrid panel
CRI-L518	22	T	2	.38	.31	130	linkage*
CRI-L1272	22	Bg	3	.40	.31	131	linkage
CRI-R657	22	T	2	.40	.36	134	hybrid panel
CRI-C88	X	M	2	.14	.14	20	sex-linkage
CRI-L1391	X	M	3	.48	.48	86	sex-linkage
CRI-R393	X	T	2	.34	.34	49	sex-linkage
CRI-S232	X	E	>7	.90	.90	138	sex-linkage

Enzymes are: B, BamHI; Bg, BglII; E, EcoRI; H, HindIII; Hc, HincII; M, MspI; P, PstI; R, RsaI; T, TaqI. Alleles is the number of different alleles present in the parents of the CEPH families screened, Het is the proportion of these parents that are heterozygotes, and PIC is polymorphism information content (Botstein et al., 1980). Meioses is the number of informative meioses in the parents in the CEPH families studied. Assignment lists whether the locus detected by the probe was initially assigned to the indicated chromosome via hybrid panels, or via linkage to previously assigned loci. An asterisk indicates that the initial two-point LOD score exceeded 3.0, but fell below the more stringent threshold of 4.0. The probes on chromosomes 7 and 16 isolated from the screening of libraries enriched for these chromosomes are described in detail elsewhere (Barker et al., 1987; T. Keith et al., unpublished data). Probes designated with the letter R are random probes from the Charon 4A library; with the letter L, probes from this library screened for single-copy human inserts; with the letter S, probes from the chromosome 7–specific library, some of which did not lie on chromosome 7; with the letters P and O, probes from the phage and cosmid libraries enriched for chromosome 16; with the letter C, probes from a total genomic cosmid library (D. Bowden, unpublished data); with the letters T, U, and V, probes from libraries propagated in recombination-deficient hosts.

Table 2. Physically Localized Anchor RFLP Loci

Locus	Probe	Location	Enzyme(s)	Alleles	Het	PIC	Meioses	Reference
AT3	pAT3	1q23-q25	P	2	.43	.36	143	Prochownic et al., 1983
REN	pHRnES1.9	1p21-qter	H	2	.50	.40	164	Hobart et al., 1984
CRYGP1	p5G1	2q33-q35	M	2	.29	.24	81	Meakin et al., 1985
D2S1	L2.30	2p25	Bg, M	4	.69	.48	223	Lothe et al., 1986
D2S5	IMR32-6	2p16-p15	M	2	.38	.26	116	Shiloh et al., 1985
D2S6	pXG-18	2q32-q36	T	2	.62	.43	219	Davatelis,1985
D3S1	HS3	3q12	H	2	.40	.31	122	Zabel et al., 1983
D3S2	p12-32	3p21-p14; 3q21-qter	M	2	.38	.29	118	Barker et al., 1984
D3S4	B67	3pter-q21	T,M	5	.45	.38	154	Morle et al., 1984
ADH3	pADH73	4q21-q25	M	2	.26	.24	84	Smith et al., 1984
HEXB	pHexB43	5q13	P	2	.10	.10	32	O'Dowd, 1985
DHFR	CHB203	5q11.1-q13.2; 5q23	M	2	.19	.17	60	Anagnou et al., 1984
HPRTP2	plambda500	5p14	M	2	.31	.24	89	Patel et al., 1984
COL1A2	NJ-3	7q21.3-q22.1	E,M,T	12	.21	.19	87	Tsipouras et al., 1983
MET	pmetD, H	7q21-q31	T	7	.62	.55	223	Cooper et al., 1984
D7S8	pJ3.11	7q22	M	2	.52	.33	183	Cooper and Schmidtke, 1985
TCRB	pT10	7q32; 7q35-q36	Bg	2	.50	.33	153	Berliner et al., 1985
PLAT	pCGE217	8p12	Hc, P	4	.43	.36	136	CRI
ABL	pablK2	9q34	P	2	.24	.17	74	Srinivasan et al., 1981
D9S1	pHF12-8	9pter-q11	T	2	.26	.21	82	Naylor et al., 1984
IRBP	H.4 IRBP	10p11.2-q11.2	Bg, M	4	.19	.19	67	Liou et al., 1987
PLAU	pCGE194	10q24-qter	Bg	2	.31	.24	101	CRI
VTR.4	VTR4.1	10q26	E	9	.38	.38	120	Colb et al., 1986
D11S16	p32-1	11p13	M	3	.52	.50	173	Feder et al., 1985
SEA	clone 3	11q13	H	2	.33	.26	97	D. Smith, personal comm.
CAT	pINT-800	11p13	T	2	.17	.14	50	Quan et al., 1986
PRB1	pPRPII2.2RP	12p13.2	E	5	.81	.81	256	Azen et al., 1984
D13S1	p7F12	13q12-q14	M,T	4	.64	.55	203	Cavenee et al., 1984
D13S3	p9A7	13q22-qter	H	2	.26	.24	84	Cavenee et al., 1984
D13S4	p1E8	13q31	M	2	.60	.43	179	Cavenee et al., 1984
D14S1	pAW101	14q32.2	E	8	.74	.71	242	Wyman et al., 1982
D15S1	pMS1-14	15q15-q21	M	2	.62	.45	201	de Martinville et al., 1984
D15S2	pDP151	15q15-q22	E	2	.40	.38	131	Brissenden et al., 1986
D15S3	pJU201	15	Bg	3	.50	.38	166	Cooper et al., 1985
HBA1	3'HVR	16p13	M	>10	.93	.93	347	Higgs et al., 1981
D17S2	L1.31	17	Bg	4	.38	.38	115	Schwartz et al., 1985
D17Z1	p17H8	17cen	E	2	.19	.17	70	Willard et al., 1986
MYH2	p10-3	17p13	M	3	.38	.33	109	Leinwand et al., 1983
NGFR	PE51	17q21-q22	Hc	2	.40	.38	133	Chao et al., 1986
D18S1	pHF12-62	18	T	2	.57	.38	163	Naylor et al., 1984
D18S3	B74	18p11.3	M	2	.50	.40	163	Morle et al., 1984
APOC2	pCII-711	19cen-q13.2	T	2	.38	.29	137	Jackson et al., 1984
D19S7	p4.1	19cen-q13.2	M	2	.52	.43	172	Shaw et al., 1986
D19S8	p17.1	19cen-q13.2	T	2	.33	.31	105	Shaw et al., 1986
D19S9	p1J2	19cen-q13.2	E	2	.19	.19	66	Shaw et al., 1986
D20S4	pMB1-27	20q13.2	M	2	.43	.38	148	de Martinville et al., 1984
D20S5	pRI2.21	20p12	M	2	.45	.38	141	Goodfellow et al., 1987
D20S6	pD3H12	20p12	T	2	.48	.38	155	Goodfellow et al., 1987
BCEI	pS2	21q22.3	B	2	.17	.14	59	Jakowlew et al., 1984
D21S15	GMG21S1	21q21.2-qter	M	4	.50	.43	160	Stewart et al., 1984
D21S17	pGSH8	21q21.2-qter	Bg	2	.40	.33	128	Stewart et al., 1984
SOD1	pS61-10	21q22.1	M	2	.12	.12	36	Lieman-Hurwitz et al., 1982
D22S10	22C1-18	22	T	3	.29	.24	87	Hofker et al., 1985
SIS	pSM-1	22q12.3-q13.1	H	2	.45	.33	144	Clarke et al., 1984

Column headings are as defined in Table 1. Where two conflicting physical localizations have been reported for a locus, both are listed, separated by a semicolon. The reference CRI indicates gene probes that were isolated at Collaborative Research. The locus SIS is also known as PDGFB.

cus could be uniquely placed in the map, then the locus with the smallest number of permissible orders was added to the map, and the entire procedure repeated, with succeeding loci tested in each position with respect to each permissible order. Frequently, the number of permissible orders increased in the initial stages of map construction but decreased when succeeding loci were added, as combined data from many loci resolved ambiguities cooperatively.

In the second strategy, a set of informative loci separated at intervals of roughly 10–20 centiMorgans were chosen, based on two-point distance calculations. All pos-

Table 3. Polymorphic Loci from CEPH Database

Locus	Location	Meioses	Reference
PGM1	1p22.1	199	White et al., 1985a
FY	1p21-q23	154	"
RH	1p36.2-p34	163	"
ACP1	2p25	112	"
GC	4q12-q13	194	"
MNS	4q28-q31	180	"
D6S5	6p24-q12	64	Leach et al., 1986
D6S7	6pter-p24	86	"
D6S8	6p21.3	123	"
D6S10	6p	169	"
GLO1	6p21.31-p21.1	150	"
HLAB	6p21.3	55	"
HLADQA	621.3	136	"
HLADRA	6p21.3	83	"
ABO	9q34.1-q34.2	99	White et al, 1985a
AK1	9q34.1-q34.2	38	"
ORM	9q34.3	190	"
D11S12	11p15.5	110	"
HBBC	11p15.1	107	"
HRAS1	11p15.5	239	"
INS	11p15	207	"
D6S9	11	115	Leach et al., 1986
D13S1	13q12-q14	125	Leppert et al., 1986
D13S2	13q22	153	"
D13S3	13q22-qter	112	"
D13S4	13q31	163	"
D13S5	13q12-q22	86	"
D13S6	13q12-q22	58	"
D13S7	13q12-q22	31	"
D13S10	13q14	19	"
ESD	13q14.11	37	"
HP	16q22.1	165	White et al., 1985a
SE	19	52	"
DXS3	Xq21.1	35	Drayna et al., 1985
DXS9	Xp22	19	"
DXS15	Xq28	72	"
DXS41	Xp22.2-p22.1	45	"
DXS42	Xq24-q26	55	"
DXS43	Xp22.2-p22.1	57	"
DXS51	Xq27-qter	77	"
DXS52	Xq28	117	"
DXS143	Xpter-p22	51	"
HPRT	Xq26-q27.3	31	"
F9	Xq26	56	"
F8C	Xq28	44	"
DXYS1	Xq21.1	64	Page et al., 1982

Meioses is number of informative meioses in the parents in the CEPH families studied. D6S9 is the locus detected by the probe p3C7, which was isolated from a chromosome 6–specific library and thus assigned a designation on chromosome 6. In fact, it lies on chromosome 11 by our linkage studies and by the hybrid panel results of Leach et al. (1986).

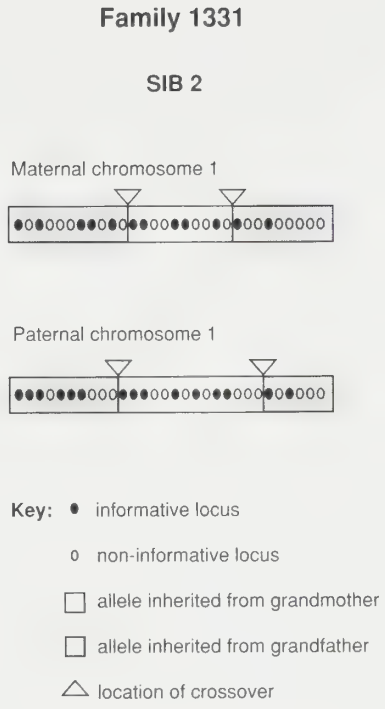


Figure 2. Grandparental Origins of Alleles at 30 Loci on Chromosome 1 in Sibling 2 of CEPH Reference Family 1331

Black ovals correspond to informative loci, white ovals to noninformative loci. A grey stippled region indicates inheritance from the grandfather, while a white region indicates inheritance from the grandmother. Each of the chromosomes 1 inherited by this child apparently underwent two crossover events, the approximate position of which is indicated by the triangle.

sible orders of these loci were tested by multipoint analysis. By trying several possible sets, it was usually possible to find a set of loci for which one order was strongly favored over all alternatives (by an odds ratio of 10,000:1). Remaining markers were then tested in each interval determined by this framework of loci and assigned to an interval when favored by 100:1 odds; markers assigned to the same interval were then ordered by computing likelihoods for all possible orders. The process was repeated, since the addition of loci to the framework made it possible to place further loci uniquely. Loci that could not be placed uniquely were assigned to all intervals that could not be excluded by the 100:1 odds test, and simultaneous comparisons of all loci within a given region of the map were performed to further resolve orders. As a test of the final order, the maximum likelihood multipoint maps were computed for the various possible permutations of consecutive marker triplets embedded in the order.

Once maps were constructed, we used a computer program to picture the grandparental origins of the alleles in each chromosome under study (Figure 2). These pictures provided strong intuitive support for the genetic orders determined, because they usually indicated fewer than three crossovers per chromosome. When anomalies were observed, such as double-crossovers involving just a single probe, the data were rechecked and, where questions remained, additional Southern blots were prepared and the genotypes determined again; in this way, several data errors were corrected.

For most chromosomes, a majority of the loci fell into a

unique genetic order, while most of the remaining loci were assigned to two or three adjacent intervals in the unique order. Throughout the linkage analysis, sex-specific recombination fractions were allowed for each interval; final maps were also generated in which the recombination fraction in each interval was not permitted to vary between the sexes. Recombination fractions were converted to centiMorgans via the Kosambi mapping function (see Ott, 1985). The distances we report must be regarded as only rough approximations, because the number of meioses is relatively small by the standards of experimental organisms, because the correct mapping function for human is unknown, and because recombination distances probably vary with age and genetic background, as they do in Drosophila (Bridges, 1927), maize (Chang and Kikudome, 1974), and other organisms.

As a final step, the linkage maps were oriented relative to the cytogenetic map of the chromosome whenever there were two or more probes whose genetic order could be resolved and whose cytogenetic positions were known and nonoverlapping. The genetic maps did not conflict with the subchromosomal assignments, except in two cases. The location of the locus D2S6 has been reported to lie at chromosome position 2q32–q36 (Davatelis, 1985); our linkage data place it genetically near D2S5, which has been localized to 2p16–p15, and far away from CRYG, which has been localized to 2q33–q35. The conflict between the genetic data and the published physical localization remains to be resolved. Also, ORM has been physically localized to the distal tip of chromosome 9q in 9q34.3, while the ABO blood group has been indirectly assigned to 9q34.1–q34.2 on the basis of tight linkage to a physically assigned locus. Our genetic data place ABO distal to ORM.

Recombinational Map of the Human Genome

The genetic maps of the 23 chromosomes are shown in Figure 3, along with chromosome ideograms to indicate the placement of those loci that have been physically localized to subchromosomal regions. The maps indicate the estimated genetic distances obtained both when separate male and female recombination fractions are allowed for each interval and when only a single recombination fraction is allowed. Uncertainties in the genetic order are indicated.

Sex Differences in Recombination

A striking general feature of the linkage maps is the difference in recombination rates between the sexes: the genetic map of the autosomes is roughly 90% longer in females than in males, although this estimate must be regarded as only approximate. Statistical tests (see Experimental Procedures) confirm that the overall sex-specificity of recombination is highly significant. Of course, male and female meioses occur in entirely different tissues and there is a priori no reason why recombination rates would be expected to be identical. Even in organisms such as maize, in which a single individual produces both male and female gametes, sex differences are observed in recombination rates (Rhoades, 1941; Carlson, 1977; Robertson, 1984). Haldane asserted as a general rule that, in organisms with a chromosomal mechanism of sex determination, the genetic length is shorter in the heterogametic sex (Haldane, 1922), and this rule applies well to many organisms, including Drosophila melanogaster, in which males (XY) show no recombination (Morgan, 1914), the moth Bombyx mori, in which females (ZW) show no recombination (Maeda, 1939; Tazima, 1964), and Mus musculus, in which certain intervals show up to twice as much recombination in females (XX) as in males (XY) (Davisson and Roderick, 1981). Increased recombination in human females was first observed in linkage studies between the ABO blood group and nail-patella syndrome (Renwick and Schulze, 1965), and has been observed since for a number of intervals in RFLP linkage maps constructed for autosomal regions. Our findings confirm that the phenomenon is quite general in humans: our linkage map indicates a substantial female excess for all autosomes except chromosome 14 (no female excess) and chromosome 10 (an 18% female excess). Substantial sex differences may exist for these chromosomes as well, but may have avoided detection because of limited sample size or incompleteness of the maps.

Despite the strong overall tendency to greater genetic length in females, the increase clearly appears to be nonuniform: many intervals appear much larger in female meiosis, others are consistent with roughly equal lengths, and a handful show increased recombination in males. As an extreme example, the loci R365 and L962 on chromosome 11q, which are jointly informative in a large number of meioses, show 0% recombination in females and 17% recombination in males (chi-squared = 13.1; $p < .0008$). (These recombination fractions are based on two-point analysis of the loci. As shown on the map, multipoint analysis yields similar, but slightly different values: 3% in females and 23% in males, with the additional female distance inferred indirectly from linkage to other loci.) In view of the large number of intervals being studied and the varying amounts of data for different intervals, however, one must be cautious about the significance of a result for any particular interval; a detailed statistical analysis of these data will appear elsewhere. However, the most effective way to test the suggestion of increased male recombination in some intervals will now be to study these same regions in a second, independent set of meioses. Longer male genetic distance has also previously been reported for a distal region of 11p in humans (White et al., 1985a) and for certain intervals in mouse (Davisson and Roderick, 1981). In maize, for which genetic lengths are generally longer in male meiosis, some intervals are reported to be longer in female meiosis (Robertson, 1984). Inhomogeneity in the ratio of female to male genetic length would suggest that, rather than sex differences being the result solely of generalized increase in the *trans*-acting recombinational machinery in human females, sex-specific chromosomal sites for recombination may exist throughout the genome (White et al., 1986). Although a special case, the human pseudoautosomal region provides one example of a clear inhomogeneity: this small region, in which the X and Y chromosomes recombine in male meiosis, measures about 50 cM in male mei-

osis but only about 5 cM in female meiosis (Rouyer et al., 1986; Page et al., 1987).

How Much of the Genome Is Covered?

The probes isolated in the random genomic screen provide an empirical estimate of the fraction of the DNA in the genome linked to the map. Of 208 probes isolated from screening of whole genomic libraries, only five (i.e., 2.4%) fail to show linkage to another locus in the map with a LOD score exceeding 3.0. Assuming that the randomly isolated RFLPs are representative, we therefore estimate that the probability exceeds 95% that a newly isolated RFLP of a similar degree of polymorphism will be detectably linked to the map. Assuming that probes detecting RFLPs are representative of DNA in the human genome (i.e., that there are not vast stretches poor in polymorphism or unclonable), we estimate that 95% of the DNA in the human genome is detectably linked to the map.

The linkage groups themselves also indicate the degree of coverage of the genome. Single, coherent linkage groups emerge for most of the chromosomes, with typically one unlinked probe that presumably lies in distal regions. The largest chromosomes are fairly densely covered, while a few of the smaller chromosomes have more rudimentary maps. We must now direct attention to filling in gaps such as those that occur on chromosome 14, which is represented by two small, unlinked linkage groups, and chromosome 19, on which none of our random probes detected loci and whose map spans only a short genetic distance.

While a random kilobase of DNA has a 95% chance of being linked, it would also be of interest to know the chance that a random centiMorgan of the genome is detectably linked. Since genetic and physical distances need not be proportional, one would expect that a screen of randomly isolated DNA probes should systematically underrepresent regions of genetic map expansion; i.e., regions in which a relatively high degree of recombination occurs in a relatively short physical stretch of DNA. Using cytogenetic distance as a proxy for physical distance (direct determination of which awaits the availability of physical maps of genomes), studies in a number of organisms report or suggest that genetic map expansion occurs in the distal portions of autosomes: in Drosophila melanogaster, genetic map expansion is evident in the distal half of each autosomal arm (Morton et al., 1976; Lindsley and Sandler, 1977); in the nematode worm Caenorhabditis elegans, genes identified by mutation are tightly clustered in the center of the genetic map and quite sparse toward the ends, strongly suggesting map expansion (Herman, 1987); and in maize, the distal 30% of the cytogenetic length of the short arm of chromosome 4 contains roughly two-thirds of the genetic length, and the distal 50% of the cytogenetic length of the short arm of chromosome 1 has yet even to be placed on the genetic map, with distal map expansion the presumed reason (E. Coe, personal communication). In humans, detailed studies of the distribution of chiasmata (the presumed cytological manifestations of crossing-over) show a significant excess near the telomeres (Laurie and Hulten, 1985a, 1985b). The most completely studied case is chromosome 1, in which the distal 15% of the chromosome contains 40% of all chiasmata (Hulten et al., 1982). Similarly, in the construction of a detailed RFLP linkage map of chromosome 21q, Tanzi and colleagues have recently found that 40% of the observed genetic length corresponds to the distal 10% of the cytogenetic arm (R. Tanzi, personal communication). Our own data for chromosome 21 show a similar effect: the loci BCE1 and SOD1 both lie in 21q2 yet are separated by an estimated genetic distance of 41 cM. Similarly, our map of chromosome 10 suggests map expansion at the distal end of 10q, in the region between PLAU and VTR.

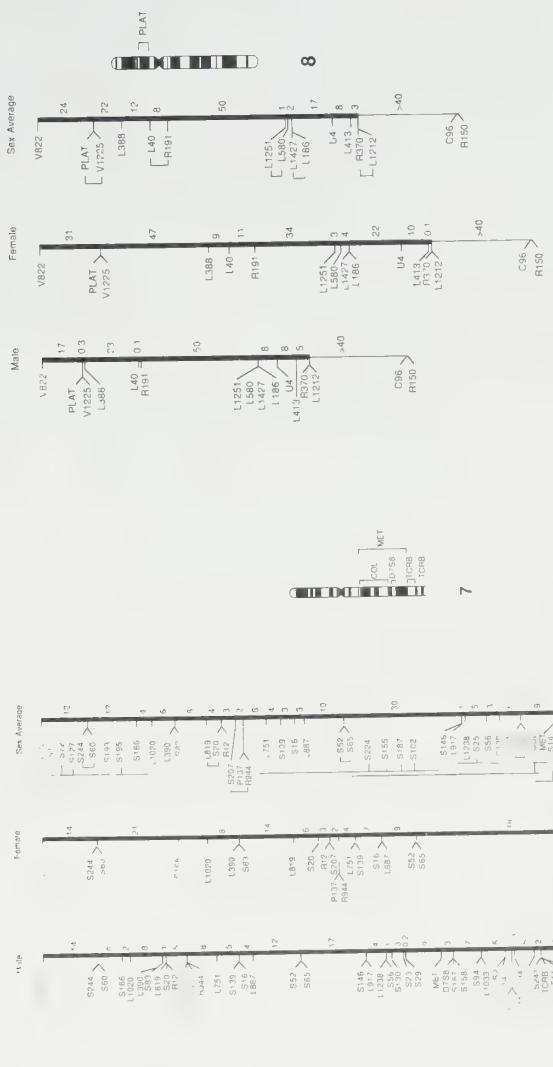
Table 4 shows the estimated minimum genetic distances observed in our map for each autosome, as well as estimates that have been obtained from counts of chiasmata in male meiosis (Morton et al., 1982; Laurie and Hulten, 1985a, 1985b). It is difficult to draw a strict comparison because, on the one hand, our estimates are simply lower bounds, which must be adjusted upward in some way to account for "end effects" and for the presence of some syntenic but as-yet-unlinked loci, and because, on the other hand, substantial methodological uncertainties still exist about counting chiasmata. Nevertheless, a rough comparison can be made. The minimum male genetic length contained within the linkage groups is about 80% of the estimate based on chiasmata counts. The results are broadly consistent with what one would expect if the documented cases of distal map expansion are taken as a rule: namely, single, large linkage groups that somewhat underestimate the total genetic length because they cannot detect linkage to the most distal regions. If we take into account the as-yet-unlinked probes known to lie on certain chromosomes, our estimate of the genetic length spanned by the mapped loci increases. Allowing a somewhat arbitrary distance of 30 cM between the linkage groups and unlinked loci would expand the estimated male length contained within the limits of the map to 2377 cM, or roughly 92% of that expected. Such close agreement is accidental, however, since the genetic lengths of the most densely covered chromosomes exceeds the estimates, while the genetic lengths of the more poorly represented chromosomes fall short.

Distribution of Polymorphism

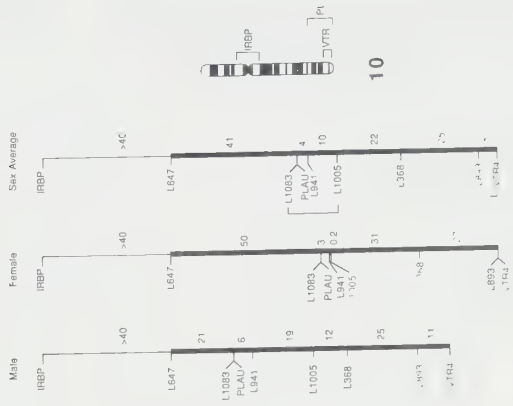
The RFLPs identified in the random genomic screen seem to lie somewhat disproportionately on the larger chromosomes: while chromosomes 1–12 contain about 70% of the cytogenetic length of the genome, some 85% of the randomly isolated RFLPs fell on these chromosomes (Table 5). The same trend is seen for each of the genomic libraries screened, the figures being 84%, 92%, and 92% for the Charon 4A library, the cosmid library, and the library propagated on recombination deficient hosts. The smaller chromosomes may in fact contain fewer polymorphisms per kilobase; alternatively, it is possible that cytogenetic length systematically overestimates the actual physical length in DNA base pairs of the smaller chromosomes.

Only three RFLPs from whole genomic libraries were identified on the X chromosome. This was expected, since the design of the random screen was systematically biased against polymorphisms on X: the libraries under-


Male
Female
Sex Average
L1046
L1209
L336
R275
L1039
C52
RH
L56
L931
L943
R629
PGM1
S182
L816
L1201
L589
L423
R1002
L1226
FY
L1054
AT3
L673
L112
REN
R117
L461
L744
L1191
L501
L1199
Male
Female
Sex Average
D2S1
ACP1
L301
D2S6
R40
L1247
P16b
L625
C13B
R322
L452
L22
L1202
L34
L523
L586
P20
C43
C36
R4
L1287
C84
CRYGP1
RH
PGM1
FY
AT3
REN
1
2


Sex Average
Female
Male
PLAT
V822
V1225
L388
L40
R191
L1251
L580
L427
L186
U4
L413
R370
L1212
C96
R150

8


Sex Average
Female
Male
IRBP
L647
L1083
PLAU
L941
L1005
L368
VTR

10

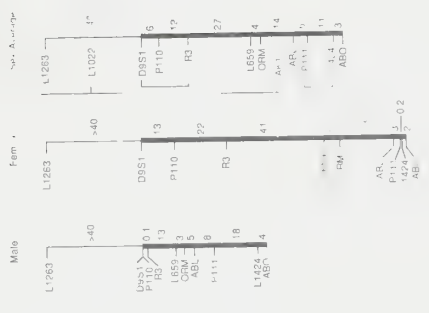
MET
D7S8
TCRB

7


ABO

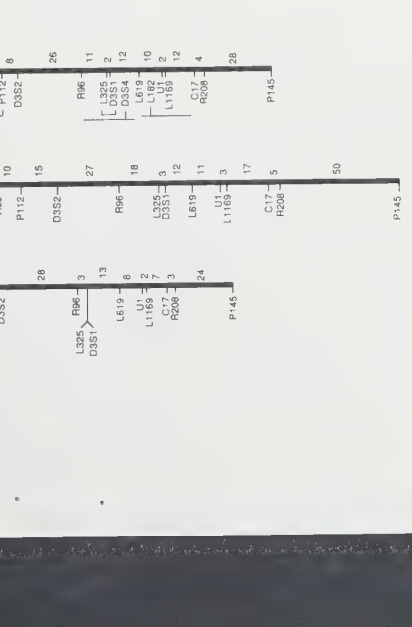
9


Sex Average
Female
Male


Sex Average
Female
Male
L1263
L1022
D9S1
P110
R3
L659
ORM
AR
P111
ABO
L1424


Sex Average
Female
Male
L892
R532
L162
R59
P112
D3S2
L325
D3S1
L619
U1
L1169
C17
R208
P145

3


D3S2
D3S4
D3S1

GC
ADH3
MNS

4

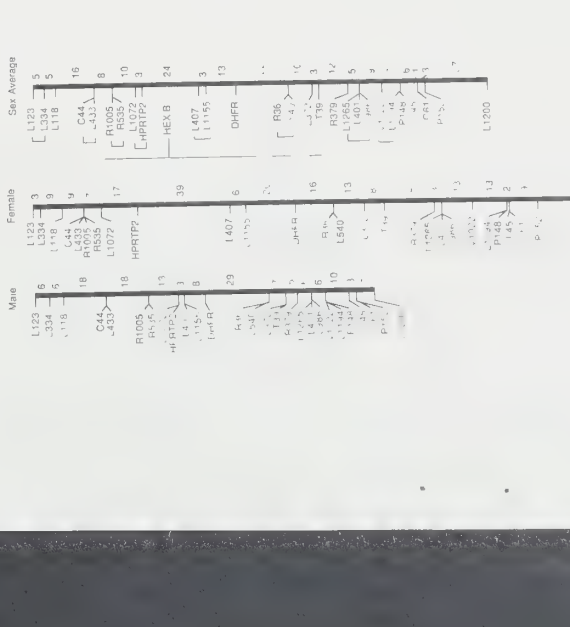
Sex Average
Female
Male
C47
L114
L1408
L1210
R171
L1190
R234
GC
R107
V820
ADH3
L503
R227
L527
R622
MNS
L231
C82


Sex Average
Female
Male
D6S7
D6S8
D6S10
R125
HLA B
HLA DR
HLA DQ
GLO1
L171
L320
D6S5
R368
P74
L994
T22
L1077

6

HPRTP2
DHFR
HEXB

5


Sex Average
Female
Male
L123
L334
L118
C44
L433
R1005
R535
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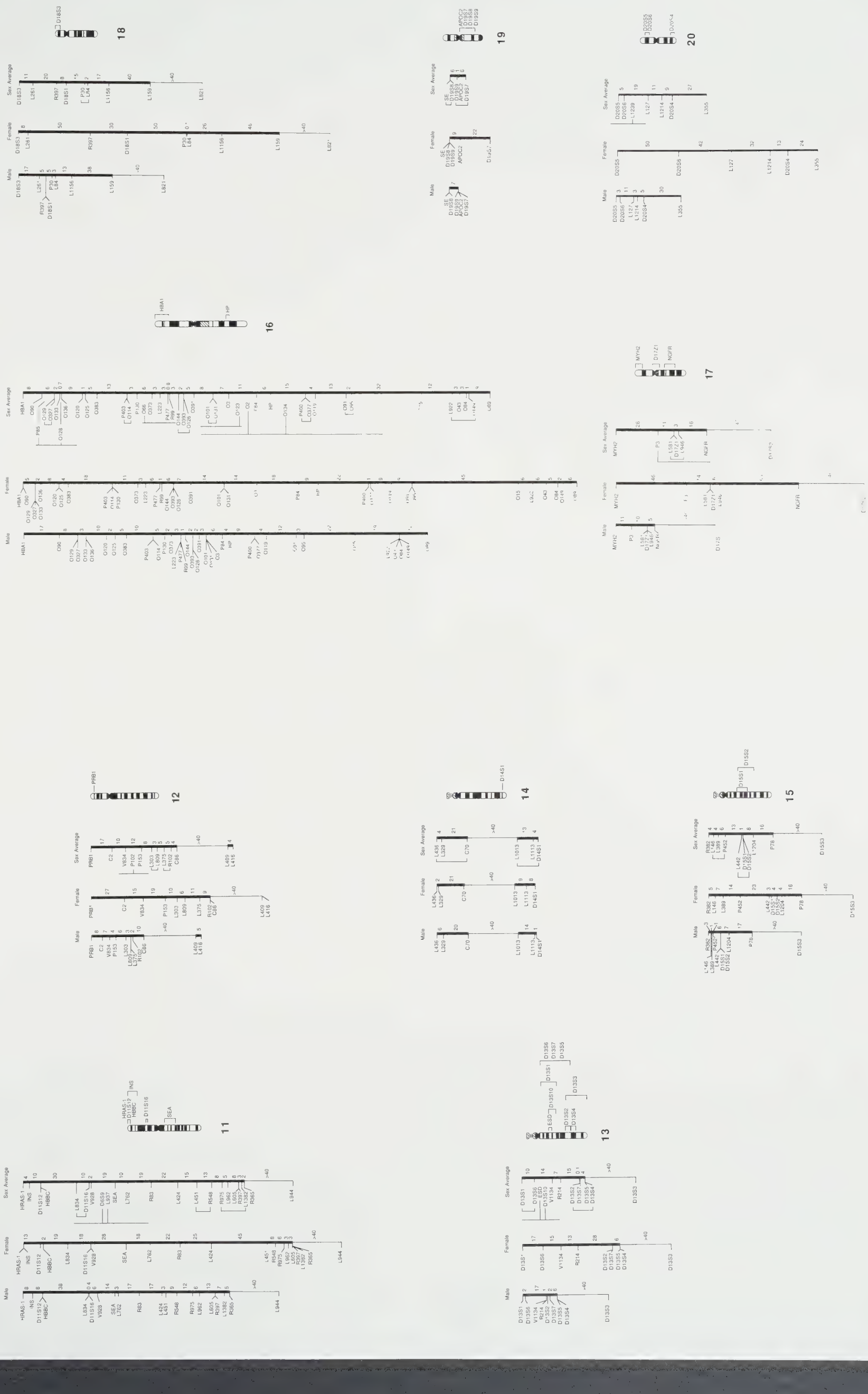
L1155
DHFR
R36
L47
R379
T99
L1265
L60
L1200


16
HBA1
HP
Sex Average
Female
Male
17
MYH2
D17Z1
NGFR
18
D18S3
19
APOC2
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D19S8
D19S8
20
D20S5
D20S6
11
HRAS-1
INS
D11S12
HBBC
D11S16
SEA
12
PRB1
13
D13S1
D13S6
D13S10
D13S1
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14
D14S1
15
D15S2
D15S1

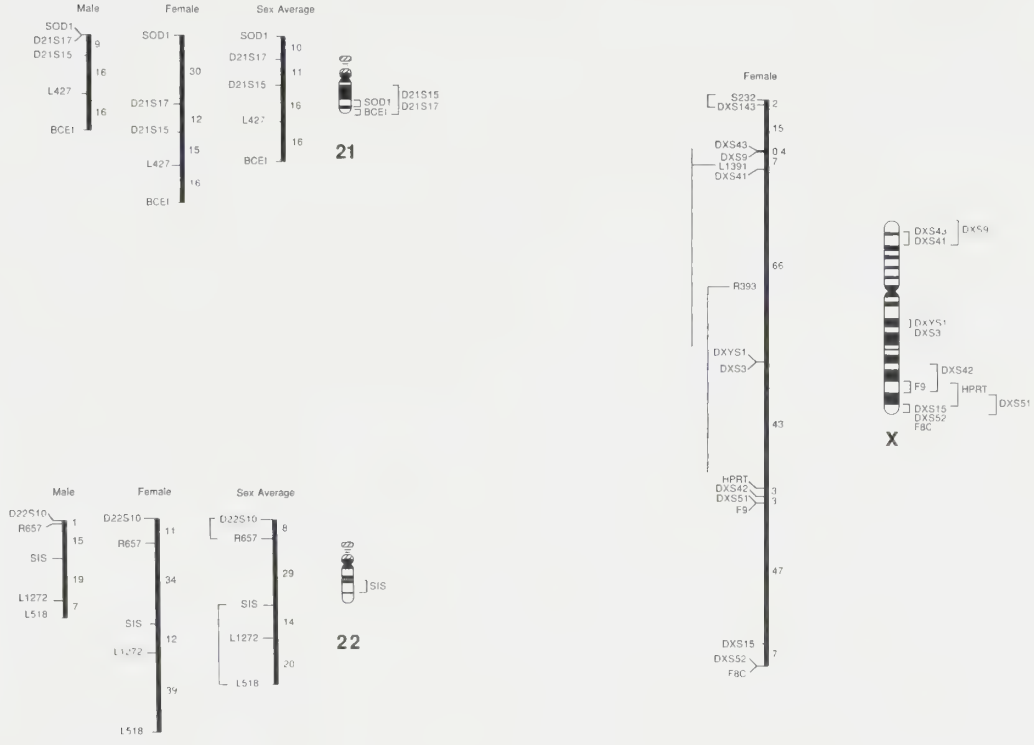

Figure 3. Genetic Linkage Maps for 23 Human Chromosomes

Loci are arranged in their most likely order, with map distances indicated in Kosambi centiMorgans. Male and female distances are estimated by allowing the recombination fraction in each interval to vary between the sexes in the linkage analysis. "Sex-average" distances are obtained by repeating the linkage analysis with the constraint that the recombination fraction in each interval be equal for males and females; the "sex-average" distances are thus not simply the mean of the corresponding male and female distances. (Even though two loci are linked, the estimate for the recombination fraction in one sex, typically the female, can occasionally be quite large. Because the mapping function is extremely imprecise for large recombination fractions, we have truncated all distances at a maximum of 50 cM, corresponding to roughly 38% recombination.) The locus order indicated is favored over alternative orders by odds of at least 100:1, with exceptions indicated (on the sex-average map only) as follows: brackets enclose a set of loci whose mutual order cannot be resolved if 100:1 odds are required; when the genetic position of a locus is poorly resolved relative to the neighboring region, a thin line to the left of the chromosome indicates its range of possible positions, using the 100:1 odds test. When the thick bar representing the genetic map narrows to a thin line between two loci, this indicates that no linkage is genetically detectable between the loci; such lines merely record the fact that the loci on either side lie on the same chromosome. The minimum distance between such "unlinked" loci cannot be determined with any accuracy; given the number of meioses and the informativeness of the loci, we estimate that most such loci must be separated by at least 40 cM, and have arbitarily indicated the genetic distance as > 40. Thirteen of the loci on the X chromosome were previously analyzed and reported (Drayna et al., 1984). Accepting this order, we have determined the location of the three additional CRI probes mapped. Subchromosomal assignment of physically localized loci is indicated to the right of the chromosome ideograms. When there are two or more loci whose genetic and physical positions have been determined and do not overlap, the genetic linkage map has been oriented relative to the physical chromosome. If such information is available for only a single locus but it lies near the telomere, we show the larger part of the linkage map pointing proximally.

Table 4. Predicted and Observed Genetic Lengths

	Predicted	Contained in Map		
	Male	Male	Female	Sex Avg.
1*	195	199	371	282
2*	173	140	236	180
3	150	151	235	180
4	138	108	292	201
5	137	139	252	192
6*	131	122	185	151
7	136	173	275	219
8*	131	111	171	147
9*	115	51	110	83
10*	127	94	111	109
11*	110	166	210	180
12*	137	45	97	68
13*	88	28	79	50
14*	88	42	40	42
15*	96	35	76	52
16	108	164	237	195
17*	109	26	116	56
18*	98	81	210	113
19	97	7	31	13
20	99	52	161	71
21	54	41	73	53
22	60	42	96	71
X	-	-	193	-
TOTAL	2577	2017	3857	2708

Estimated genetic lengths (Morton et al., 1982) are based on counts of chiasmata in male meiosis. The observed genetic lengths are the total distances contained between the lock in linkage groups. An asterisk indicates that the chromosome contains a locus or loci not yet demonstrably linked to the main linkage group; the complete collection of loci on the chromosome must in fact span a larger genetic interval than that shown. All distances are in centiMorgans.

Table 5. Chromosomal Distribution of Loci

	"Anchor" Loci			
		Linkage Data Collected At		
Chromosome	CRI RFLPs	CRI	CEPH	Total
1	27	2	3	32
2	24	4	1	29
3	14	3	0	17
4	16	1	2	19
5	25	3	0	28
6	11	0	8	19
7	59	4	0	63
8	15	1	0	16
9	7	2	3	12
10	6	3	0	9
11	15	3	5	23
12	11	1	0	12
13	2	3	6	11
14	5	1	0	6
15	7	3	0	10
16	40	1	1	42
17	3	4	0	7
18	7	2	0	9
19	0	4	1	5
20	4	3	0	7
21	1	4	0	5
22	3	2	0	5
X	4	0	13	17
Total	306	54	43	403

represented X, being derived from males, and the blots used for polymorphism screening underrepresented X, since they included males. In addition, the X chromosome has been shown to contain a several-fold lower density of polymorphism (Hofker et al., 1986).

Interestingly, the most informative of the RFLPs show a tendency to cluster near the ends of the linkage map. Considering those identified in the random screen that have heterozygosity greater than 0.70, we find that 11 of 28 (39%) lie within the terminal 5% at either end of the genetic linkage map, whereas one would expect only two or three. We speculate that increased polymorphism in the most distal regions of the chromosomes may be related to increased recombination in these regions, since the recombination system itself has been implicated in the generation of mutations (Brandenburger et al., 1981; Thomas and Capecchi, 1986). Further support for this notion is provided by the pseudoautosomal region, in which recombination is tremendously enhanced relative to physical distance and in which polymorphism appears to be especially abundant (Cooke et al., 1985; Goodfellow et al., 1986; Page et al., 1987; Simmler et al., 1985).

Many of the issues raised will require further study to resolve. More precise understanding of the differences in recombination rate between the sexes, more precise estimates of recombinational distances, and the resolution of local ambiguities of order will require that the genetic markers be studied in many further meioses. Correlation of the genetic and cytogenetic maps, which will shed light on the issue of distal map expansion, will require physical localization of many of the markers on the genetic map via in situ hybridization of subclones containing unique sequence, linkage mapping of many more probes whose physical location is already known, or both.

Conclusion

When we began this project some five years ago, we reasoned that the most efficient way to construct a comprehensive genetic map of the human genome was to isolate and study random polymorphic loci, rather than to proceed chromosome by chromosome. Genetic maps fall together cooperatively: when a sufficiently high density of loci is reached, linkage maps emerge for all the chromosomes at once. Recently, we reached this point. We should emphasize, however, that this genetic linkage map represents only an initial step. Some regions are relatively poorly covered, and must now be filled in. Moreover, considerably more detailed genetic maps should now be constructed, since the power of a genetic map increases considerably with its density.

The current map should be of immediate value for several purposes, including:

(a) Systematic Mapping of Simple, Single-Gene Disorders
By selecting a panel of about 100–200 probes throughout the genome, one can efficiently search nearly all regions

of the genome to locate the cause of any single gene disorder. Given the density and informativeness of the markers in the map and the additional information provided by multipoint linkage analysis, calculations show that there is a high likelihood of being able to map any single-gene disorder for which about 20–25 phase-known meioses are available, provided of course that the locus lies within the 95% of the genome currently linked.

(b) Initial Efforts to Map Diseases with Complex Modes of Inheritance

Without a map, it is difficult to map heterogeneous diseases caused by mutations at any one of several loci, since evidence for linkage to a particular locus in one family is offset by evidence against linkage in another family. Such genetic complexities become more tractable for linkage analysis if inheritance data for the whole genome are analyzed simultaneously (Lander and Botstein, 1986b). The current map is sufficient to begin such approaches, although a denser map would increase their efficiency.

(c) Systematic Deletion Mapping of Recessive Oncogenes, through Study of the Loss of Heterozygosity in Tumor Cells

A number of types of tumors, such as retinoblastoma (Cavenee et al., 1985), Wilm's tumor (Fearon et al., 1984), bilateral acoustic neuroma (Seizinger et al., 1986), and colon cancer (Solomon et al., 1987) are associated with deletions of particular chromosomal regions, which presumably expose recessive oncogenes. The availability of a full panel of probes will facilitate screening of new tumor types, by comparing DNAs from tumor tissue and peripheral blood for the loss of an allele at a polymorphic locus. Systematic screening of the genome will guard against the possibility of being misled by the nonspecific aneuploidy found in many tumors. In addition, the limits of deletions can be defined to within the resolution of the map.

(d) Rapid Assignment of Newly Discovered Polymorphisms to Chromosomes

The data underlying the linkage map characterize the pattern of inheritance (i.e., grandmaternal or grandpaternal allele) at many loci throughout the genomes of the children in the CEPH families studied. The pattern of inheritance of any new probe can now be used to identify at once its approximate chromosomal location (with at least 95% chance of success), just as is done in mapping with recombinant inbred strains in mouse. The approach can serve as a complement or an alternative to methods of physical assignment, such as in situ hybridization.

With a sufficiently dense linkage map, rare recessive disease genes can be mapped by using the DNA of inbred affected children to perform homozygosity mapping (Lander and Botstein, 1987), even when few families are available with multiple affected children. The current map is adequate to support preliminary efforts of this sort, but it is sparser and less evenly spaced than desirable (except in the case of chromosomes 7 and 16.) Increasing the density of the markers by a factor of 2–3 would be desirable, in order to take full advantage of these methods.

A genetic map consisting of markers spaced no more than 5 cM apart would be desirable, in order to take full advantage of the power of linkage mapping. In the current map, the average spacing is roughly 10 cM, and many intervals are considerably larger. Since a similar mapping project of comparable scope using the CEPH families is currently underway in the laboratories of our colleagues in Salt Lake City (White et al., 1985a), we expect that a linkage map of twice the average density will result when the data from the two groups are combined. Together with the data from other groups constructing detailed linkage maps of more limited chromosomal regions, a truly complete genetic linkage map of humans will emerge.

(Note: The probes and data generated in this study will be made available to interested investigators for research purposes.)

Experimental Procedures

Pedigree DNAs and Hybrid Panels

Human DNA samples from three-generation families (typically having four grandparents, both parents, and six to 15 children) were provided by CEPH, the Centre d'Etude du Polymorphisme Humain in Paris, for CEPH families 12, 66, 1332, 1334, 1344, 1346, 1349, 1413, 1416, 1418, and 1421. DNA from families 884, 13291, 13292, 13293, 13294, 1331, 1333, 1340, 1341, 1345, 1350, and 1362 was prepared as described (Bell et al., 1981) from transformed lymphoblast lines, which were purchased from the Camden Cell Repository or were a gift from R. White. These families comprise 310 individuals; the children in them represent a total of 362 meioses. Hybrid panels used for assigning probes to chromosomes were provided by J. Frezal and colleagues and by T. Shows and colleagues.

DNA Probes

DNA probes were isolated from a total human genomic bacteriophage library (Lawn et al., 1978), a total human genomic cosmid library prepared in the vector C2RB (Bates and Swift, 1983), two phage libraries of human DNA flow-sorted for chromosomes 7 and 16, respectively (Van Dilla et al., 1986), a chromosome 16 cosmid library prepared from a rodent–human hybrid cell line bearing chromosome 16 as its only human chromosome, and three bacteriophage libraries, numbered 185, 285, and 1284, grown on hosts designed not to select against repetitive sequences (Wyman et al., 1986). Previously reported gene probes, which were used to assign linkage groups to chromosomes, are described in Table 2.

RFLP Identification and Pedigree Analysis

Human clones were tested for restriction fragment length polymorphism by hybridization to Southern blots of DNA from five unrelated individuals. Each DNA sample was digested with six or more of the restriction endonucleases BamHI, BglII, EcoRI, HincII, HindIII, MspI, PstI, RsaI, and TaqI using the conditions specified by the suppliers (New England Biolabs and BRL) except that 2–5 U/μg of DNA was used in overnight digests and MspI digests were carried out at 20°C to minimize partial digestion. Four micrograms of the resultant DNA fragments were resolved according to size by horizontal gel electrophoresis in 0.8% agarose at 3 V/cm overnight in Tris-acetate buffer, and, after staining with ethidium bromide for direct visual inspection, the DNA fragments were denatured in situ with 0.2 N NaOH. The DNA fragments were transferred to a nylon filter support (Zeta-Bind, AMF/Cuno, Meriden, CT) by Southern blotting, and fixed to the filter by baking at 80°C. DNA probes were labeled with [^{32}P]-dATP or dCTP by nick translation. Bacteriophage lambda clones used as hybridization probes were grown and DNA prepared as described (Helms et al., 1985). Cosmid DNAs were prepared by alkaline lysis of minipreps (Ish-Horowitz and Burke, 1981) or the closed circular DNA purified by CsCl/EtBr density centrifugation. Probes were hybridized to the filters in 10% dextran sulfate, 1 M NaCl, 100 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.1% sodium pyrophosphate, 0.5% sarkosyl, 0.5 mg/ml heparin, and 30% formamide, except that probes not known to be free of human repeated sequences were prehybridized with unlabeled human DNA (Litt and White, 1985) to block the hybridization of repeated sequences

to the membrane-bound DNA. The filters were washed twice at room temperature in 2× SSC for a total of 30 min, followed by two 65°C washes of 30–60 min each in 0.1× SSC, 0.2% SDS, and were exposed to X-ray film (Kodak XAR-5) with an intensifying screen (Dupont Cronex Lightening Plus) for 1–5 days at −80°C. DNA probes were stripped from the membranes in 0.1 N NaOH. The nylon membranes could be reused up to 25 times.

Candidate probes for polymorphic loci were hybridized to Southern blots of DNAs from parents of CEPH families to confirm the observed polymorphic pattern and to indicate which families were informative for linkage analysis. Analysis of the inheritance of RFLP loci by Southern hybridization was conducted on the informative families. Experimental conditions were identical to those used for RFLP identification and characterization as described above.

Linkage Analysis

Multipoint linkage analysis was performed using two independently written computer programs, CRI-MAP and MAPMAKER (Barker et al., 1987a; Lander et al., 1987). Both programs implement new techniques for maximum likelihood multipoint linkage analysis (Lander and Green, 1987), but use different strategies to find the marker order. Both programs are available from the authors. Multipoint analysis was performed without taking interference into account. The significance of sex differences in two-point crosses was evaluated by means of a likelihood ratio test. The significance of the overall sex difference seen in multipoint maps was evaluated by means of a permutation test: as a robust test of whether the likelihood increase resulting from allowing sex-specific parameters was statistically significant or, instead, simply the result of doubling the number of parameters to be fit, we computed the corresponding likelihood increase for 100 examples in which the sex of the parents had been randomly permuted, but the data were otherwise identical.

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Notes Added in Proof

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Collaborative Research Incorporated

October 15, 1993

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

Dear Alfred:

It was wonderful seeing you again last night. The meeting suddenly turned the clock back forty-five years to the basement at Converse at Harvard a long time ago.

As promised I'm sending the enclosed packet of information on Collaborative Research, Inc. which I believe will give you a sense of what the Company is as we begin refashioning it into a dynamic instrument for the discovery of new pharmaceuticals in the new era in which we are now entering. We have the money to survive but we do not have the financial resources that are needed to enable us to develop the new drugs on our own rather than to seek partnerships with the pharmaceutical industry.

In any event, if you are interested I think you would be well served by a visit where you could see what we do first hand.

In any event, when next you come to Boston with your dear wife let me know as Laurel and I would be delighted to get together with you.

Best regards.

Sincerely,

Orrie M. Friedman

100 Beaver Street, Waltham, Massachusetts 02154
617- 487-7979
FAX 617/487-7960

Robert J. Hennessey
President and Chief Executive

August 23, 1993

To Our Shareholders:

On June 30, 1993, less than three months after Collaborative announced its intention to sell the Company's diagnostic testing business, we completed the sale of the division to DIANON Systems, Inc., a recognized market leader in the cancer and genetic testing business. This action, we are pleased to note, has improved Collaborative's financial position and has consequently given us the time and opportunity to implement the Company's core strategy of licensing, discovering and developing genetically-based proprietary therapeutics and pharmaceuticals.

In this letter, I would like to briefly review with you the reasons for our decision to sell Collaborative Diagnostics and to apprise you of our strategy and prospects going forward.

Background: Within weeks of my arrival at Collaborative Research in March, it became apparent to me that, despite the Company's best efforts over the past several years to grow and develop the diagnostic testing business, our options with respect to this division were limited. Approximately two thirds of Collaborative's monthly cash loss, a cash drain that we simply could not afford to sustain, was directly attributable to this business. As I saw it, our viable options were the following: close the laboratory, maintain it in the hope that it became self-sustaining before our cash ran out, or seek a reputable buyer.

Closing the business would have been regrettable, considering the Company's past investment in the business and the outstanding capabilities and excellent reputation of the laboratory and its staff. Taking into account the continuing need for investment and development, the option of waiting for the division to reach break even was simply too high risk to be feasible. The decision, therefore, was an easy one: we had no alternative but to sell.

The Result: The resulting benefits to Collaborative Research are very positive: with this divestment, and an accompanying trimming of our corporate staff to match the reduced headcount, we added funds to our treasury and reduced our cash burn rate significantly. This relieves the financial pressure upon the Company. We can now focus our time, attention and resources on the implementation of the Company's core strategy.

Looking Ahead: Collaborative Research's strategy is now well defined and clearly focused: We are applying advances from the human genome research to the development of proprietary drugs for the treatment of infectious diseases and other major diseases. Specific projects that are receiving priority attention are tuberculosis, manic depression, asthma and a variety of cancers.

We are pursuing a three-pronged approach for the implementation of this strategy:

- continuing basic molecular genetic research and development, complemented by licensing in proprietary technologies that will strengthen and add value to those we are already utilizing to pursue this research;

- developing strategic alliances with major pharmaceutical and biomedical partners for the joint development of therapeutics and pharmaceuticals for the treatment of infectious diseases and other major diseases; and

- sustaining our base revenue stream of research contracts and grants – by both continuing to seek awards from government agencies focused on our core research areas, and by aggressively seeking additional corporate research contracts. These corporate research contracts will have their own benefits: they will have higher margins than government contracts; they will reduce our reliance on government funding; and they may lead to key strategic partnerships of the kind we are seeking. Last month we announced our first such contract: an agreement with Abbott Laboratories that will take advantage of Collaborative's well developed capabilities in large-scale DNA manipulation and sequencing and expertise in gene cloning.

Third Quarter Results: The Company's results for the third quarter of fiscal 1993 are included on the opposite page. For the three months and nine months ended May 29, 1993, total revenues increased 17 and 20 percent, respectively, compared to the same periods last year. The net loss increased for both periods, reflecting the investment we had been making in building the diagnostic testing business.

In closing, let me share with you my optimism and confidence in the Company's future. We believe that we can compete successfully in the pursuit of our core strategy because of our years of pioneering work, expertise and competence in the field of genetically-based drug development. We also believe that the current market valuation of the Company is not consistent with the valuation of other companies who have similar technology, but who can not match either our record of technical accomplishment or expertise. We are hopeful that the market will soon recognize this discrepancy. In the meantime, we continue to be grateful to all of our shareholders for your trust and confidence.

Sincerely,

Robert J. Hennessey
President and Chief Executive Officer

Consolidated Balance Sheets

(Figures in thousands)

	(Unaudited) May 29, 1993	August 31, 1992
Assets		
Cash and Short-term Investments	$ 3,783	$ 7,144
Other Current Assets	668	623
Equipment and Leasehold Improvements – net	866	785
Goodwill	772	803
Total	$ 6,089	$ 9,355
Liabilities and Shareholders' Equity		
Current Liabilities	$ 1,161	$ 1,998
Deferred Compensation	201	163
Capital Lease Obligations	259	275
Shareholders' Equity	4,468	6,919
Total	$ 6,089	$ 9,355

Summary of Operations

(Unaudited)

(Figures in thousands except per share amounts)

	Thirteen Weeks Ended	
	May 29, 1993	May 30, 1992
Revenues:		
Operating Revenue	$ 1,758	$ 1,414
Interest Income	33	109
Royalties	48	55
Total Revenues	$ 1,839	$ 1,578
Costs and Expenses	2,550	2,003
Net Loss	$ (711)	$ (425)
Net Loss per Common Share	$ (.07)	$ (.04)
Weighted Average Number of Shares Outstanding	10,664	10,663

	Thirty-Nine Weeks Ended	
	May 29, 1993	May 30, 1992
Revenues:		
Operating Revenue	$ 4,452	$ 3,562
Interest Income	140	285
Royalties	98	55
Total Revenues	$ 4,690	$ 3,902
Costs and Expenses	7,140	5,391
Net Loss	$(2,450)	$ (1,489)
Net Loss per Common Share	$ (.23)	$ (.14)
Weighted Average Number of Shares Outstanding	10,664	10,662

Collaborative Research Incorporated

100 Beaver Street
Waltham, Massachusetts 02154
617- 487-7979

Consolidated Balance Sheets

(Dollars in thousands)

	[illegible]	[illegible]
Assets		
Cash and Short-term Investments	$ [illegible]	$ [illegible]
Other Current Assets	[illegible]	[illegible]
Equipment and Leasehold Improvements, net	[illegible]	[illegible]
Goodwill	[illegible]	[illegible]
Total	$[illegible]	$[illegible]
Liabilities and Shareholders' Equity		
Current Liabilities	$ [illegible]	$ [illegible]
Deferred Compensation	[illegible]	[illegible]
Capital Lease Obligations	[illegible]	[illegible]
Shareholders' Equity	[illegible]	[illegible]
Total	$[illegible]	$[illegible]

Summary of Operations (Unaudited)

(In thousands, except per share amounts)

	Thirteen Weeks Ended	
	February [illegible]	February [illegible]
Revenues:		
Operating Revenue	$1,310	$1,[illegible]
Interest Income	50	[illegible]
Royalties	25	0
Total Revenues	$1,385	$1,[illegible]
Costs and Expenses	2,353	1,737
Net Loss	$ (968)	$ (570)
Net Loss per Common Share	$ (.09)	$ (.05)
Weighted Average Number of Shares Outstanding	[illegible]	[illegible]

	Twenty-Six Weeks Ended	
	February 27, 1993	February 2[illegible]
Revenues:		
Operating Revenue	$2,694	$2,148
Interest Income	106	176
Royalties	[illegible]	[illegible]
Total Revenues	$[illegible]	$[illegible]
Costs and Expenses	[illegible]	[illegible]
Net Loss	$[illegible]	$[illegible]
Net Loss per Common Share	$ [illegible]	$ [illegible]
Weighted Average Number of Shares Outstanding	[illegible]	[illegible]

Collaborative Research at a Glance

Collaborative Research, Inc. is a [illegible] firm engaged in large-scale genome mapping and DNA sequencing. It pursues [illegible] discovery through its research [illegible] cloning the relevant genes for major human disorders including tuberculosis, leprosy, non-insulin dependent diabetes, medullary thyroid carcinoma, facioscapulohumeral (FSH) muscular dystrophy, schizophrenia, asthma, hypertension and prostate cancer.

Collaborative Research Incorporated

1[illegible] Beaver Street
Waltham, Massachusetts 02154
617-[illegible]

Collaborative Research Incorporated

Second Quarter Report 1993

2

To Our Shareholders:

Immediately following the release of our second quarter financial results, Collaborative announced a change in strategic direction for the Company. Collaborative will deploy its resources, experience and financial resources to pursue a core strategy of licensing, discovering and developing genetically based proprietary therapeutics.

Our new strategic focus capitalizes on the substantial strengths of the Company's human and molecular genetics organization with its well developed capabilities in genetic mapping, sequencing and DNA-related research efforts. To implement this strategy, we have accelerated our efforts to both in-license complementary early-stage technology and forge a series of product development alliances with major pharmaceutical and biomedical partners.

As we implement our strategy, we are giving priority attention to such projects as tuberculosis drug screening methodologies, cardiology and a variety of cancers. Collaborative believes that its large-scale systems for genetic mapping and sequencing may represent a valuable resource to major pharmaceutical firms who are pursuing disease genes, but whose in-house research efforts can be broadened and accelerated by Collaborative's high throughput potential.

The Company's strategic refocussing has led to our decision to seek a buyer for Collaborative Diagnostics, our genetic and cancer testing business. Although these fields are attractive, this decision is required to reduce the significant cash losses incurred by the Company during the past twenty-four months in our efforts to grow this business. The financial commitment required for a successful growth strategy in cancer and genetic diagnostic testing falls well beyond available resources. We are actively engaged in serious discussions with a number of potential buyers, and are hopeful that we will have further developments to report imminently.

Financial Results: Operating revenues increased 21 percent for the second quarter of fiscal 1993 compared to the same period last year. The revenue growth is attributable to continued growth of both the research and diagnostic testing businesses. Costs and expenses also increased, largely due to the continued investment in the diagnostic testing business, resulting in an increase in the net loss for the quarter to $.28 per share, compared to a loss of $.15 per share for the second quarter of fiscal 1992. For the first half of the year, operating revenue grew 25%, compared to the same period a year ago. The net loss increased from $.40 per share in 1992 to $.71 per share in 1993. The Company's cash and marketable securities were $15 million at the end of the second quarter.

We are hopeful that this refocussing of Collaborative's strategy, coupled with the sale of Collaborative Diagnostics, will substantially reduce the cash drain and provide the most promising prospects for the future growth and prosperity of the Company. We appreciate your support as we pursue this strategy.

Sincerely,

Orrie M. Friedman
Chairman of the Board

Robert J. Hennessey
President and Chief Executive Officer

May 5, 1993

Newsbriefs:

ROBERT J. HENNESSEY APPOINTED CEO AND ELECTED TO BOARD

In March, Robert J. Hennessey joined Collaborative Research, Inc. as President, Chief Executive Officer and a member of the Board of Directors, reporting to Collaborative's Board. Orrie M. Friedman, Ph.D. continued to serve as Chairman.

A well known strategic deal maker in the biopharmaceutical industry, Mr. Hennessey has more than twenty-five years of strategic planning, acquisition, licensing and strategic partnering experience in pharmaceuticals and biotechnology. For the past two and a half years, Mr. Hennessey served as President of Hennessey & Associates, LTD., a private consulting firm specializing in strategy development and deal structuring. He previously served for ten years as Corporate Vice President of Sterling Drug, in charge of strategic planning, acquisitions and licensing. Prior to Sterling, he held senior staff or operating positions with Abbott Laboratories, SmithKline and Merck.

COLLABORATIVE RECEIVES TWO ADDITIONAL RESEARCH AWARDS

Collaborative Research scientists received two new research awards from federal agencies beginning April 1, 1993.

Development of Genetic Linkage Maps for Human Chromosomes 10 and 20: Collaborative has received a Phase II Small Business Innovation Research (SBIR) grant to complete the development of high resolution, genetic maps for human chromosomes 10 and 20. The award from the National Center for Human Genome Research is worth $500,000 over a two-year period. Such genetic maps will facilitate the localization and ultimate cloning of disease genes.

Sequencing of DNA Samples: Collaborative has been awarded a contract to search for mutations in samples of DNA provided by the National Institute of Environmental Health Sciences. The contract is for one year with four one-year options, and is worth nearly $100,000 the first year.

Consolidated Balance Sheets

(Figures in thousands)

	(Unaudited) November 28, 1992	August 31, 1992
Assets		
Cash and Short-term Investments	$5,547	$7,144
Other Current Assets	717	623
Equipment and Leasehold Improvements – net	874	785
Goodwill – net	793	803
Total	$7,931	$9,355
Liabilities and Shareholders' Equity		
Current Liabilities	$1,246	$1,998
Deferred Compensation	175	163
Capital Lease Obligations	363	275
Shareholders' Equity	6,147	6,919
Total	$7,931	$9,355

Summary of Operations (Unaudited)

(Figures in thousands except per share amounts)

	Thirteen Weeks Ended November 28, 1992	November 30, 1991
Revenues:		
Operating	$1,384	$1,064
Interest Income	56	93
Royalties	25	0
Total Revenues	$1,465	$1,157
Costs and Expenses	2,237	1,651
Net Loss	$ (772)	$ (494)
Net Loss per Share	$ (.07)	$ (.05)
Weighted Average Number of Shares Outstanding	10,664	10,662

Collaborative Research at a Glance

Collaborative Research, Inc. is the leading U.S. firm in large-scale genome mapping and sequencing. Through Collaborative Diagnostics, the firm conducts advanced DNA diagnostic testing. The firm also pursues patentable drug discovery for major human disorders by cloning the relevant genes for tuberculosis, leprosy, non-insulin dependent diabetes, medullary thyroid carcinoma, FSH muscular dystrophy, bipolar affective disorder, asthma, hypertension and prostate cancer.

Collaborative Research Incorporated

100 Beaver Street
Waltham, Massachusetts 02154
617-487-7979

Collaborative Research Incorporated

First Quarter Report 1993

To Our Shareholders:

During fiscal 1993, Collaborative Research, Inc. is continuing to focus on the implementation of the Company's strategy to build its complementary businesses of research directed towards new drug discovery and the diagnosis of diseases with a genetic component. Total revenues for the first quarter of fiscal 1993 grew 27 percent, compared to the same period last year, reflecting the continued strong growth of both of these businesses.

Financial Results: The research and diagnostic testing businesses grew 28 percent and 36 percent, respectively, during 1993's first quarter, compared to the same period in fiscal 1992. The year's first quarter revenues also included estimated quarterly royalty income of $25,000 from The Dow Chemical Company, resulting from sales of recombinant chymosin. Costs and expenses, as a percent of operating revenues, increased by 6% for the first quarter when compared to the same period last year, primarily due to the addition of certain essential management personnel and facility relocation costs associated mostly with the building of the diagnostic testing business. These increased costs and expenses resulted in an increase in the net loss to $.07 per share for the first quarter of fiscal 1993, compared to a net loss of $.05 per share for the first quarter of fiscal 1992. We ended the quarter with cash on hand and short-term marketable securities of $5.5 million.

Collaborative Diagnostics: Over the past year, we put into place the infrastructure of technology, management and facilities that will enable us to achieve substantial continued revenue gains in fiscal 1993 and improved operating results over the next few years. We are currently directing our activities towards increasing revenues by leveraging our current testing capabilities to develop relationships with potential large customers. We are in the process of forming alliances with several large regional cytogenetic laboratories, as well as a nationally recognized teaching hospital, which would enable us to open distribution channels not previously accessible to us. We are also actively pursuing a number of other key large customer accounts, including a national hospital consortium, a major cancer screening diagnostics company and a major Japanese diagnostics company.

Contracts and Grants: Collaborative Research continues to aggressively pursue additional government sponsored contracts and grants to augment the more than $12 million in multi-year awards secured over the past two years. These awards enable us to focus our efforts towards the potential commercial development of diagnostics and therapeutics for specific diseases, and to develop leading edge technology applicable to the Human Genome Initiative. The Company retains patent rights for the commercial applications of the products and processes developed under these contracts and grants. We are continuing to actively pursue partnerships with major pharmaceutical companies who have an interest in developing diagnostics or therapeutics related to specific diseases. We are quite hopeful that we will reach agreement with at least some of them, as this is the direction in which new drug development must inevitably proceed.

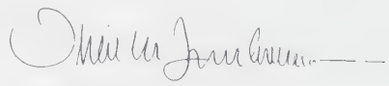
New Phase II SBIR Awarded: We were recently awarded a Phase II Small Business Innovation Research (SBIR) grant by the National Institute of General Medical Science. The $500,000 two-year award, which began January 1, 1993, is directed toward developing a faster, more convenient DNA diagnostic test technology which will simultaneously examine many different regions of many different genes. Collaborative scientists will first build and validate such a multiplex DNA diagnostic test for a large number of the most commonly found mutant alleles of the CFTR gene, the gene which is responsible for cystic fibrosis (CF). This CF test will be useful in population screening as well as for diagnosis of CF mutations in members of families with a history of cystic fibrosis. The convenience, speed and virtually limitless potential for multiplexing make this new test format superior to and less expensive than currently available DNA-based diagnostic tests. In addition, it will permit several different tests to be done at the same time on the same test sample.

Annual Shareholder Meeting Held: At Collaborative's Annual Meeting of Shareholders, held recently in Boston, I called upon members of Collaborative's senior management team to present an overview of the year just past. These presentations included the highlights discussed above.

My remarks focused on the significance of the transition the Company has made over the past year since the sale of the Biomedical Products Division. The Company is now focussed entirely in an area that has limitless commercial potential — that is, molecular DNA, an area which reflects the Company's highest level of expertise. We have applied our expertise and our resources to two key areas related to this field — drug discovery and diagnostics — and we have put into place the technology, the organization and the strategy that will enable us to participate in the commercial opportunities related to these areas in a substantial way.

I indicated that now is the time to bring on board a CEO who shares our vision and who has a proven track record of performance in the pharmaceutical industry. Our search firm has identified several attractive candidates, and we are hopeful that we can reach agreement in the near term. I believe that we are now strategically positioned to achieve the highly successful and profitable status we seek.

Sincerely,



Orrie M. Friedman
Chairman and Chief Executive Officer

February 16, 1993

COLLABORATIVE RESEARCH, INC.

NOTICE OF SPECIAL MEETING OF SHAREHOLDERS IN LIEU OF AN ANNUAL MEETING

To Be Held On January 25, 1993

To the Shareholders of
COLLABORATIVE RESEARCH, INC.

NOTICE IS HEREBY GIVEN that a Special Meeting in Lieu of an Annual Meeting of Shareholders of Collaborative Research, Inc. (the "Company") will be held on January 25, 1993 at 1:00 p.m. at The Bank of Boston, 100 Federal Street, Boston, Massachusetts, for the following purposes:

A. To elect five directors.

B. To ratify the selection of Arthur Andersen & Co. as the Company's auditors for the fiscal year ending August 31, 1993.

C. To transact such other business as may properly come before the meeting or any adjournments of the meeting.

The Board of Directors has fixed the close of business on November 30, 1992 as the record date for the determination of shareholders entitled to notice of and to vote at this meeting and at any adjourned session(s) thereof.

All shareholders are cordially invited to attend the meeting. However, to assure your representation at the meeting, you are urged to mark, sign, date and return the enclosed form of proxy as promptly as possible. Shareholders attending the meeting may vote in person even if they have returned a proxy.

By Order of the Board of Directors

DAVID C. CHAPIN, *Clerk*

December 21, 1992
Boston, Massachusetts

COLLABORATIVE RESEARCH, INC.

PROXY STATEMENT

INFORMATION CONCERNING SOLICITATION AND VOTING

General

The enclosed proxy is solicited by the Board of Directors of Collaborative Research, Inc. (the "Company") for use at a Special Meeting in Lieu of an Annual Meeting to be held on January 25, 1993, or at any adjourned session(s) of that meeting, for the purposes set forth in the foregoing Notice. The cost of solicitation of proxies, including expenses in connection with preparing and mailing this Proxy Statement, will be borne by the Company. This solicitation of proxies is being made by mail, although it may be supplemented by telephone, facsimile or personal solicitation by directors, officers, or other regular employees of the Company. No additional compensation will be paid to such individuals for such services. This Proxy Statement and accompanying proxy will be mailed on or about December 21, 1992, to all shareholders entitled to vote at the meeting.

A copy of the Company's 1992 Annual Report to Shareholders, including financial statements, is being mailed concurrently with this Proxy Statement to each shareholder entitled to vote at the meeting.

Voting Rights and Outstanding Shares

Any shareholder giving a proxy has the power to revoke it at any time before it is exercised. It may be revoked by filing with the Clerk of the Company an instrument of revocation or a duly executed proxy bearing a later date. It may also be revoked by attending the meeting and electing to vote in person.

Only shareholders of record at the close of business on November 30, 1992, will be entitled to notice of and to vote at the meeting. As of November 30, 1992, the Company had outstanding 10,664,166 shares of Common Stock, $.10 par value (the "Common Stock"), each of which is entitled to one vote.

Security Ownership of Certain Beneficial Owners and Management

The following table sets forth, as of November 30, 1992, certain information regarding all shareholders known by the Company to be the beneficial owners of more than 5% of the Company's Common Stock, and the stock ownership of the Company's current directors and nominees, and of all directors and officers of the Company as a group:

Name of Beneficial Owner(1)	Amount and Nature of Beneficial Ownership	Percent of Class
Orrie M. Friedman	3,227,256(2)	30.26%
Mark D. Friedman	147,483(3)	1.38%
Lawrence Levy	50,000(3)	*
Seymour Rothchild	50,000(3)	*
Paul C. Zamecnik	149,737(3),(4)	1.40%
The Dow Chemical Company	777,305	7.29%
All directors and officers as a group (8 persons)	4,117,876(5)	38.61%

(1) The address of all such persons is c/o the Company, 100 Beaver Street, Waltham, Massachusetts 02154, except The Dow Chemical Company ("Dow"), whose address is Dow Center, Midland, Michigan 48640.

(2) Includes 263,562 shares owned by, or in trust for, certain members of Dr. Friedman's family (other than Mark D. Friedman). Dr. Friedman disclaims beneficial ownership of these shares.

(3) Includes 25,000 shares for Dr. Zamecnik and 50,000 shares for each of Dr. Rothchild and Messrs. Friedman and Levy which may be issuable upon the exercise of outstanding options, subject to certain vesting requirements.

(4) Includes 18,925 shares owned by Dr. Zamecnik's wife. Dr. Zamecnik disclaims beneficial ownership of these shares.

(5) Includes a total of 665,600 shares which may be issuable upon the exercise of outstanding options, subject to certain vesting requirements, granted to certain directors and officers. Also includes 282,487 shares as to which certain of the directors and officers disclaim beneficial ownership.

Section 16(a) of the Securities Exchange Act of 1934 requires the Company's executive officers and directors, and persons who beneficially own more than ten percent of the Company's stock, to file initial reports of ownership and reports of changes in ownership with the Securities and Exchange Commission and the New York Stock Exchange. Executive officers, directors and greater than ten percent beneficial owners are required by SEC regulations to furnish the Company with copies of all Section 16(a) forms they file.

Based solely on a review of the copies of such forms furnished to the Company and written representations from the Company's executive officers and directors, the Company believes that during fiscal 1991 and 1992 all Section 16(a) filing requirements applicable to its executive officers, directors and greater than ten percent beneficial owners were complied with, except that Paul C. Zamecnik, a director of the Company, did not timely report a transaction involving shares of Common Stock by his spouse which occurred in September, 1992.

EXECUTIVE COMPENSATION

The following table sets forth certain information as to the four executive officers of the Company, and as to all executive officers as a group, during the fiscal year ended August 31, 1992:

Cash Compensation Table

Name of Individual or Number in Group	Capacities in which served	Cash Compensation
Orrie M. Friedman	Chairman of the Board of Directors, President and Chief Executive Officer	$148,385
William P. Johnson	Sr. Vice President, Business Development	$135,000
Gerald F. Vovis	Sr. Vice President, Research and Development	$135,000
Fenel M. Eloi	Vice President, Treasurer and Chief Financial Officer	$100,000
All executive officers as a group (4 persons)		$518,385

Other Compensation Arrangements

The Company has entered into an agreement with Northern Ventures Corporation providing for the consulting services of Mr. Lawrence Levy. The agreement provides for monthly compensation of $1,500 plus out-of-pocket expenses, does not have a specified term, and is terminable by either party at any time.

The Company has entered into an agreement with Dr. Rothchild pursuant to which, for his service as a member of the Executive Committee, Dr. Rothchild receives monthly compensation of $1,500 plus out-of-pocket expenses. The agreement does not have a specified term and is terminable by either party at any time.

Directors of the Company who are not also employees receive an annual retainer of $4,000 and a meeting attendance fee of $1,000 per meeting plus out-of-pocket expenses.

Company Savings Plan

Effective March 1, 1985, the Company adopted a savings plan for the benefit of all employees. The savings plan is administered by a committee appointed by the Board of Directors of the Company, and all amounts contributed are held and invested by an independent trustee. The savings plan does not have a specified termination date. Employees may agree to salary reductions ranging from 2% to 12% of base salary. In certain circumstances, the maximum percentage may be less than 12% due to limitations imposed by the Internal Revenue Code. The salary reductions have the effect of reducing compensation for federal income tax purposes under Section 401(k) of the Internal Revenue Code. The Company matches 50% of the employee's salary reduction of 2%, and 25% of the employee's salary reduction between 2% and 6%, limited to the first $50,000 of annual base salary. The trustee invests the salary reduction amounts in selected funds as designated by the employee. Distributions are made to employees or their beneficiaries in the event of retirement or death or upon termination of employment for any other reason, subject to certain forfeiture provisions. Effective September 1, 1987, the Company's contributions under the savings plan become fully vested on an employee's third anniversary of employment with the Company. During fiscal 1992, the Company made contributions of $19,051 pursuant to the savings plan, including contributions of $1,000 for each of the accounts of Messrs. Johnson and Vovis and $2,000 for the account of all executive officers as a group.

Stock Option Plan

In 1981, the Company adopted an amended stock option plan (the "1981 Plan") pursuant to which 500,000 shares of Common Stock are reserved for issuance upon exercise of options granted to key employees. In May 1984, the number of reserved shares was reduced to 300,000. The options are granted at $.20 per share and may be subject to certain vesting requirements. As of August 31, 1992, options covering a total of 74,000 shares at $.20 per share under the 1981 Plan were outstanding, and no further options may be granted under the 1981 Plan. The difference on the date of grant between the fair market value of the Common Stock and the option price is treated by the Company as deferred compensation for accounting purposes.

The Company adopted an incentive stock option plan (the "Incentive Plan") in October 1981, pursuant to which 250,000 shares are reserved for issuance upon exercise of options granted to key employees. The options are granted at not less than the fair market value at the date of grant. As of August 31, 1992, options covering a total of 109,651 shares were outstanding at prices ranging from $1.375 to $11.94 per share, the fair market value on the date of the grant. No further options may be granted under the Incentive Plan. Of the total number of outstanding options under the Incentive Plan, options covering a total of 40,100 shares are held by the Company's executive officers and directors, and the balance is held by employees.

In May 1984, the Company adopted the 1984 Stock Option Plan (the "1984 Plan") pursuant to which 500,000 shares are reserved for issuance upon exercise of options granted to key employees and consultants. The options may be granted at prices not less than 50% of the fair market value of the Common Stock on the date of grant. The difference, if any, between the fair market value of the Common Stock on the date of grant and the option price is treated by the Company as deferred compensation for accounting purposes. As of August 31, 1992, options covering a total of 307,463 shares were outstanding at prices ranging from $.8125 to $8.50 per share. Of the total number of outstanding options under the 1984 Plan, options covering a total of

20,000 shares are held by the Company's executive officers and directors, and the balance is held by employees and consultants.

Effective October 18, 1988, the Company adopted the 1988 Stock Option Plan (the "1988 Plan") pursuant to which 750,000 shares reserved for issuance upon exercise of options granted to key employees and consultants, whether or not they are officers or directors, of the Company. The options may be granted at prices not less than 50% of the fair market value of the Common Stock on the date of grant. The difference, if any, between the fair market value of the Common Stock on the date of grant and the option price is treated by the Company as deferred compensation for accounting purposes. As of August 31, 1992, options covering a total of 551,500 shares were outstanding at prices ranging from $.875 to $2.62 per share. Of the total number of outstanding options under the 1988 Plan, options covering a total of 280,000 shares are held by the Company's executive officers and directors, and the balance is held by employees and consultants.

Effective October 28, 1991, the Company adopted the 1991 Stock Option Plan (the "1991 Plan") pursuant to which 500,000 shares are reserved for issuance upon exercise of options granted to key employees and consultants, whether or not they are officers or directors, of the Company. The options may be granted at prices not less than (a) 100% of the fair market value of the Common Stock on the date of grant in the case of incentive stock options, or (b) the par value per share of the Common Stock in the case of non-incentive stock options. The difference, if any, between the fair market value of the Common Stock on the date of grant and the option price is treated by the Company as deferred compensation for accounting purposes. As of August 31, 1992, no options were outstanding under the 1991 Plan.

Under each of the stock option plans described above, no options may be granted after ten years from the effective date of the respective plan. The Stock Option Committee of the Board of Directors determines the eligibility of employees of the Company to receive options under the Company's stock option plans.

	Fenel Eloi	William P. Johnson	Gerald F. Vovis	All Executive Officers as a Group	All Employees as a Group
Granted 8/31/91 to 8/31/92					
Number of shares	25,000	31,000	31,000	87,000	236,000
Average per share exercise price	$1.625	$.9125	$.9125	$1.15	$2.0529
Exercised 8/31/91 to 8/31/92					
Net value realized (market value less exercise price)	0	0	0	0	$960.75

The closing price of the Common Stock on December 4, 1992 was $1.75 as reported by NASDAQ.

In November 1986, Mr. Levy was granted a non-incentive stock option under the 1984 Plan covering 25,000 shares of Common Stock at an exercise price of $5.25 per share. The option vests in four annual installments commencing November 3, 1987, and terminates on November 3, 1996. In September 1989, Mr. Levy and Dr. Rothchild were granted non-incentive stock options under the 1988 Plan covering 25,000 and 50,000 shares, respectively, of Common Stock at an exercise price of $1.75 per share. The options vest in four annual installments commencing September 18, 1990, and terminate on September 18, 1999.

In October 1989, Mr. Friedman and Dr. Zamecnik were each granted non-incentive stock options covering 25,000 shares of Common Stock at an exercise price of $2.00 per share. These options, which were not granted under any existing stock option plan, were approved by the Company's shareholders at the 1989 Annual Meeting. The options vest in four equal annual installments commencing October 23, 1990, and terminate on October 23, 1999. In addition, options covering 25,000 shares at an exercise price of $4.25 per share were granted in July 1988 and are outstanding under a separate option agreement with Mr. Friedman.

PROPOSAL A

ELECTION OF FIVE DIRECTORS

It is intended that the enclosed proxy will be voted for the election of the five persons named below unless such authority has been withheld in the proxy. Each director will hold office until the next annual meeting and until his successor is elected and shall have been qualified. If any nominee should be unavailable for election at the time of the meeting (which is not presently anticipated) the persons named as proxies may vote for another person in their discretion or may vote for fewer than five directors. All of the nominees are currently directors of the Company, and all have agreed to serve as directors if elected at the meeting. All of the nominees were elected as directors of the Company at the 1992 Annual Meeting.

The nominees for directors of the Company who are proposed for election at the meeting, their ages, and a description of their principal occupations are set forth in the following table. The principal occupations and business experience of the nominees for the past five years have been with the employers indicated, although in some cases they have held different positions with such employers.

Name	Age	Principal Occupation and Other Directorships	Director Since
Orrie M. Friedman(1)(2)	(77)	Chairman of the Board, Chief Executive Officer and President; Prior to June 1989, Chairman of the Board and Chief Executive Officer; Prior to June 1986, Chairman of the Board of Directors; Prior to July 1982, President and Chief Executive Officer.	1962
Mark D. Friedman	(39)	Counsel, Mitsui & Co. (USA), Inc.; Attorney, Skadden, Arps, Slate, Meagher & Flom (law firm) 1986-1989; student, Columbia University Graduate School of Business 1984-1986; Trial Attorney, United States Department of Justice, Civil Division 1981-1984.	1988
Lawrence Levy(2)	(69)	Chairman and President of Northern Ventures Corporation (international management and business consulting firm).	1986
Paul C. Zamecnik	(80)	Principal Scientist, Worcester Foundation (a biomedical research institute); Professor of Medicine — Harvard Medical School and Director, Huntington Laboratories, and a physician at Massachusetts General Hospital prior to 1979.	1964
Seymour Rothchild(2)	(72)	Private investor, 1984 to present; Vice President, 1973-1983, of Clinical Assays (an immunoassay kit manufacturer); President and co-founder, New England Nuclear Corp. 1956-1970.	1989

(1) By virtue of his ownership of Common Stock, Dr. Friedman may be deemed to control the Company.

(2) Member of the Executive Committee.

In connection with the purchase of Common Stock by Dow in 1981, Dr. Friedman agreed that, as long as Dow owns at least 2% of the Company's outstanding Common Stock, he will vote all shares of Common Stock then owned by him and will otherwise use his best efforts to cause and maintain the election to the Board of Directors of a mutually satisfactory representative of Dow. Dow has advised Dr. Friedman that it does not wish to have a representative on the Board at this time.

The Board of Directors held 8 meetings during fiscal 1992.

The Board of Directors has established an Audit Committee consisting of Messrs. Rothchild, Levy and Zamecnik, which held 1 meeting during fiscal 1992. The duties of the Audit Committee consist of reviewing with the Company's independent auditors and its management the scope and results of the annual audit, the scope of other services provided by the Company's auditors, proposed changes in the Company's financial and accounting standards and principles, the Company's policies and procedures with respect to its internal accounting, auditing and financial controls, and making recommendations to the Board of Directors on the engagement of independent auditors.

The Board of Directors has established a Stock Option Committee, consisting of Drs. Friedman and Zamecnik and Mark D. Friedman. The duties of the Stock Option Committee consist of administering operations under the Company's stock option plans and considering the grant of stock options to employees of the Company. During fiscal 1992, the Stock Option Committee held 6 meetings.

The Board of Directors does not have a nominating committee or compensation committee.

PROPOSAL B

RATIFICATION OF SELECTION OF AUDITORS

Arthur Andersen & Co., Boston, Massachusetts, has been selected by the Board of Directors of the Company as auditors of the Company for the fiscal year ending August 31, 1993. Unless otherwise indicated, proxies will be voted in favor of ratifying the selection of Arthur Andersen as auditors. A representative of Arthur Andersen will be present at the annual meeting if requested by a shareholder (either in writing or by telephone) in advance of the annual meeting. Such requests should be directed to the Clerk of the Company.

SHAREHOLDER PROPOSALS

In order for any proposal that a shareholder intends to present at the next annual meeting of shareholders to be eligible for inclusion in the Company's proxy material for that meeting, it must be received by the Clerk of the Company at the Company's offices in Waltham, Massachusetts, no later than August 13, 1993.

OTHER MATTERS

The Board of Directors knows of no other business to be presented at the meeting, but if other matters do properly come before the meeting, it is intended that the persons named in the proxy will vote in respect thereof in accordance with their best judgment.

In the event that sufficient votes in favor of any of the proposals set forth in the accompanying Notice are not received by the time scheduled for the meeting, the persons named as proxies may propose one or more adjournments of such meeting for a period of not more than 60 days in the aggregate to permit further solicitation of proxies with respect to any of such proposals. Any such adjournments will require the affirmative vote of a majority of the votes cast on the question on person or by proxy at the session of the meeting to be adjourned. The persons named as proxies will vote in favor or such adjournment those proxies that they are entitled to vote in favor of such proposals. The will vote against any such adjournment those proxies required to be voted against any of such proposals. The costs of any such additional solicitation and of any adjourned session will be borne by the Company.

The Board of Directors encourages you to have your shares voted by signing and returning the enclosed form of proxy. The fact that you will have returned your proxy in advance will in no way affect your right to vote in person should you find it possible to attend. However, by signing and returning the proxy you have assured your representation at the meeting. Thank you for your cooperation.

Collaborative Research Incorporated

100 Beaver Street, Waltham, MA 02154
617/487-7979
FAX 617/487-7960

Corporate Profile

Collaborative Research, Inc. (CRI) is a genome-based therapeutics company. The Company is focused on discovery and development of novel therapeutic approaches to disease, capitalizing on advancements of the Human Genome Project. CRI currently operates the country's largest broad-based commercial genome research program, consisting of over 60 scientists led by 18 Ph.D.s.

CRI is a leader in the emerging field of genomics -- the discovery, analysis, and commercial development of genetic information. The Company believes the enormous information flowing from the Human Genome Project will result in a paradigm shift in pharmaceutical drug development, and provide a new set of drug discovery tools. Genomic advances will allow identification of the molecular basis of common multi-factorial diseases such as cancer, mental illness, cardiovascular disease, asthma, and many others. Genetic information will permit elucidation of the biochemical pathways responsible for these diseases, and will lead to novel therapeutic targets for intervention.

Success in genomics requires powerful interdisciplinary skills in gene mapping, DNA sequencing, and bioinformatics (computational molecular biology). Over the past few years CRI has built these core skills into a major genomics program through judicious use of government-sponsored research grants. Since 1991 CRI has been awarded over $14 million in genome-based contracts and grants. Some of the more relevant ongoing CRI projects are summarized below:

High-Throughput Multiplex Sequencing
CRI is developing and optimizing computer-assisted multiplex sequencing for large-scale applications. The technology, developed by Dr. George Church and his colleagues at the Howard Hughes Medical Institute at Harvard Medical School, can now generate nearly 10 million base-pairs of raw sequence data per year in the Company's labs. CRI is currently developing the technology under agreement with Harvard and believes that planned improvements in automation and optimization will improve multiplex throughput by at least 10-fold over the next two years. This technology can now be applied successfully to the rapid sequencing of large numbers of cDNA clones, entire genomes of pathogenic organisms, and sizable regions of human genomic DNA.

Mycobacterium tuberculosis
Sequencing the genome of M. tuberculosis is a major current research effort. CRI has already identified and applied for patents on novel TB genes associated with growth and development. These genes will present new targets for drug development.

Disease Gene Discovery
CRI is developing highly polymorphic genetic markers, constructing genetic linkage maps with these markers, and using these genetic maps to determine the chromosomal location of disease genes. Currently, CRI is using these procedures to map the gene(s) involved in manic depression and is preparing the resources to map the gene(s) involved in schizophrenia.

Physical Mapping
CRI is developing chimera-free, genomic DNA libraries and sequence-tagged sites (STSs) and using these resources to construct physical maps of human chromosomes. Currently a physical map for human chromosome 10 is being developed under a grant from the National Center for Human Genome Research.

Gene Cloning
CRI has an extensive collection of human genomic DNA and cDNA libraries which are a powerful resource for cloning disease genes. CRI is applying these resources to cloning the gene on chromosome 4q responsible for causing fascioscapulohumeral muscular dystrophy.

cDNA Mapping
CRI is developing a high-throughput, automated hybridization procedure for mapping human cDNAs to their chromosomal locations with the use of mega-base sized, yeast artificial chromosomes (YACs).

Sequence-Based Hormone Discovery
In collaboration with Immuno-Cor, CRI is utilizing proprietary predictive sequence algorithms to screen its human cDNA libraries for genes coding for novel peptide hormones.

Bio-Informatics
CRI has built a six person bio-informatics group focusing on computational molecular biology. Bio-informatics capabilities are critical for organizing, analyzing, and utilizing the massive DNA sequence information generated by genome research.

The above applications are illustrative of CRI's technological resources, with some examples of specific disease targets in current projects. CRI believes its large-scale, high-throughput systems for genetic mapping, sequencing and analysis represent a tremendous resource for translating the output of the Human Genome Project into novel pharmaceuticals, diagnostics and vaccines.

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)
_X_ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934 [FEE REQUIRED]
For the fiscal year ended: AUGUST 31, 1992

OR

___ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934 [NO FEE REQUIRED]
For the transition period from _____ to _____.

Commission file number: 0-10824

COLLABORATIVE RESEARCH, INC.
(Exact name of registrant as specified in its charter)

MASSACHUSETTS	04-2297484
(State or other jurisdiction of incorporation or organization)	**(I.R.S. employer identification no.)**
100 BEAVER STREET; WALTHAM, MASSACHUSETTS	02154
(Address of principal executive offices)	**(Zip code)**

Registrant's telephone number: (617)487-7979

Securities registered pursuant to Section 12(b) of the Act: N/A

Securities registered pursuant to Section 12(g) of the Act:
COMMON STOCK, $.10 PAR VALUE
(Title of class)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes _X_ No ___

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. [ ]

The aggregate market value of the voting stock held by non-affiliates of the registrant as of November 19, 1992 was approximately $14,633,180.

The number of shares outstanding of the registrant's common stock as of November 19, 1992 was 10,664,166.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's proxy statement for use at its Special Meeting of Shareholders in lieu of an Annual Meeting to be held on January 25, 1993 are incorporated by reference into Part III.

PART I

Item 1. BUSINESS

(a) General

Collaborative Research, Inc., (sometimes referred to as the "Company") is a biotechnology company which was organized under the laws of Massachusetts in 1961. The Company is engaged in the development, processing and marketing of diagnostic tests and services. The Company is a leader in developing DNA probe technology for the diagnosis of genetic diseases, for cancer testing and for use in personal identification. The Company is also a leading research contractor in large scale genome mapping and DNA sequencing with applications to the field of therapeutic drug discovery. The Company applies its expertise in the fields of human genetics, molecular biology, immunology, protein biochemistry and molecular genetics to its endeavors.

(b) DNA Research and Development

The Company has several diagnostic tests in various stages of research and development which it expects will have commercial applications. Due to the uncertainties inherent in such endeavors, no assurances can be given as to the timing, cost, scientific or commercial success of these research and development projects.

Genetic or DNA Markers The Company has been and is still engaged in various projects to map the human genome. These projects are based on the use of DNA probes to construct a genetic linkage map for each individual human chromosome. In 1987, the Company reported the development of what the Company believes was the first scientifically useful genetic linkage map of substantially all of the human genome. This development has provided a unique tool which has already been used to locate and subsequently clone genes responsible for causing inherited diseases and has, thus, been instrumental in developing DNA diagnostic tests for a number of common diseases which have a clear genetic component. Disease genes can be located on the map through studies of co-inheritance of the DNA markers and the disease in families afflicted with an inherited disease. Once the disease gene is located, DNA-based diagnostic tests can then be developed for these diseases in families already known to suffer from the various diseases.

Such diagnostic tests based on genetic linkage analysis allow one to follow the inheritance of DNA markers located near disease genes and ultimately predict whether an individual has inherited a disease-causing gene. The Company has demonstrated the applicability of this test method to the diagnosis of cystic fibrosis and other diseases. The Company believes that these tests will be useful both for single-gene

disorders, of which cystic fibrosis is an example, and for disorders that are known to have multiple genetic components, although the exact biological mechanisms are not yet clearly understood, such as diabetes, heart disease, hypertension and various forms of cancer. In addition, testing procedures using DNA probes to monitor bone marrow engraftment and to determine paternity and other related applications have been introduced by the Company. Patent applications have been filed covering certain of the DNA probes. See "Patents and Proprietary Technology".

The Company has secured a number of research contracts and grants from the National Institutes of Health, as well as the Department of Energy, to pursue its work in constructing genetic and physical maps of human chromosomes, mapping and cloning disease genes and determining the practicality and cost-effectiveness of innovative DNA sequencing technology. The various institutes from which the Company receives support currently, either directly and/or through contracts from universities, include the following: National Center for Human Genome Research; National Institute of Mental Health; National Cancer Institute; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Neurological Disorders and Stroke; and National Institute of General Medical Sciences. The Company continues to use its own funds to sponsor research and development of certain aspects of this technology while also seeking additional external funding for this program.

The Company currently sells many of its DNA probes to forensics and paternity testing laboratories. A sale typically includes a licensing arrangement whereby the customer pays a royalty charge for the use of each probe in addition to a small fee for the probe itself. The use of these probes in forensics and paternity testing enables users to distinguish one individual from another with greater than 99% certainty. The use of these probes will also allow determinations to be made from extremely small samples, as well as from very different sample types. The Company also provides identification testing in its own laboratories.

Rennin The Company worked for several years on producing the enzyme rennin, essential in cheese production, via genetic engineering techniques. In fiscal 1988, the U.S. Patent and Trademark Office granted the Company broad patent claims covering aspects of the production of recombinant rennin in cells, including yeast and bacteria. In addition, the Company has been granted patent protection in a number of foreign countries. See "Patents and Proprietary Technology".

This project was previously funded under a research contract with The Dow Chemical Company ("Dow") which ended during fiscal 1985. Dow has licensed the patent to Pfizer

Inc., which, with FDA approval, began selling recombinant rennin in 1990. The agreement with Pfizer provides for royalty payments to the Company based upon sales of rennin after Dow has recovered specified prior investments.

DNA Probe-Related Products In 1990, the Company signed an agreement with Health Sciences Research Institute (Hoken Kagaku Kenkyujyo) of Yokohama, Japan, under which HSRI is funding the development of a family of DNA probe-related products. The agreement also gives HSRI the exclusive Japanese distribution rights to both these new products and Collaborative's existing DNA probes. The product development agreement is aimed at accelerating the development of products required to perform genetic mapping, genetic disease diagnosis and DNA identification and to facilitate the cloning of genes.

The Company is licensing and selling certain of its DNA probes for paternity, forensics and identity use and for research in mapping the human genome. The Company's DNA probes for paternity and forensic testing are among the standards for the industry, and the Company continues to develop them for use in rapid and cost-effective assays for human identification.

(c) Collaborative Diagnostics

Collaborative Diagnostics (CD), a division of the Company, is one of the few commercial genetic reference laboratories in the world. CD is a high quality, full service testing laboratory providing state-of-the-art services to physicians for the diagnosis of cancer and inherited disease. CD currently provides services for molecular genetics, cytogenetics, biochemistry, flow cytometry and genetic counseling from its new facility in Waltham, Massachusetts.

In the area of molecular genetics, CD offers the following inherited disease molecular DNA tests: the detection of cystic fibrosis and fragile X syndrome; a presymptomatic or prenatal test for adult polycystic kidney disease; a test for the detection and analysis of the Y chromosome; a test for determining paternity; and banking of DNA samples.

Molecular genetic testing in the area of cancer includes the following tests: T-cell/B-cell clonality analysis; bcr/abl gene rearrangement; bcl-2 gene rearrangement; densitometric analysis of autoradiographs; bone marrow transplant monitoring; and leukemia cytogenetics.

Cytogenetic tests offered by CD are: amniotic fluid; peripheral blood; skin fibroblasts; products of conception; and chorionic villus sampling chromosome analysis for the

detection or validation of the existence of fragile X syndrome, Down's syndrome and neural tube defects.

Biochemical testing is performed in the screening of maternal serum which is an indicator of potential mental retardation or neural tube defects.

Flow cytometry analysis tests include both leukemia/lymphoma immunophenotyping and gene rearrangements which are useful in the diagnosis of leukemia/lymphoma.

(d) Research and Development

The Company expended $359,529, $2,300,650 and $1,956,423 during fiscal 1992, 1991 and 1990, respectively, on internally-funded research and development projects. The Company additionally received $4,179,080, $2,093,911 and $1,974,829 during fiscal 1992, 1991 and 1990, respectively, from its corporate and governmental sponsors for research and development conducted by the Company pursuant to both research contracts and grants.

Patents and Proprietary Technology

The Company diligently seeks to protect its proprietary rights in know-how and inventions, and seeks patent protection for certain products and processes where it is deemed advisable. Other patent applications may be filed by or be assigned to the Company's contract research sponsors pursuant to agreements with them. The Company has received patents for a number of processes or products both in the United States and foreign countries relating to DNA probes, rennin, EMIA, prourokinase (PUK) modifications, IL-2 and anti-calculus agent. The Company is aware that United States patents claiming IL-2 and derivatives have been issued to another party. There can be no assurance that either domestic or foreign patents will be issued on any pending application or that any patents which may be issued will be valid or have commercial benefit. Further, there can be no assurance that the Company's patents will afford protection against competition or that the patents will not be designed around or infringed upon by others. Patents have been issued to others and numerous patent applications are pending, in both the United States and foreign countries, which may affect the Company's research, development and manufacturing activities. The extent to which the Company may need to obtain licenses under these patents, if available, or design around such patents cannot be accurately determined. No assurance can be given as to the availability of any necessary licenses, the success of any challenge or the feasibility of designing around any patented product.

In 1981, the Company entered into a License Agreement (the "Agreement") with Stanford University pursuant to which the Company received a non-exclusive license under certain

patent rights involving the engineering of biologically functional replicons possessing desired genetic properties of parent DNA molecules. The Agreement requires annual minimum advance royalty payments and actual royalty payments which vary depending on such factors as type of use or product. During fiscal 1992, the Company paid minimum royalties of $10,000 to Stanford pursuant to the Agreement.

The Company has licensed, on a non-exclusive basis, from the Massachusetts Institute of Technology and the Whitehead Institute for Biomedical Research the commercial rights for the diagnostic use of a panel of DNA probes which detect regions spanning the Y chromosome. A diagnostic test utilizing these probes was introduced by the Company's Diagnostic Services Division in June 1987. The Company paid minimal royalties during fiscal 1992 pursuant to that agreement.

The Company has received a non-exclusive license from Oxford University for the use of a DNA probe in the commercial diagnosis of adult polycystic kidney disease. The Company has also received from Dr. Stephen Reeders and Dr. David Weatherall a non-exclusive license to manufacture, sub-license and sell a DNA probe with applications in paternity testing and forensic analysis. The Company paid minimal royalties during fiscal 1992 pursuant to those agreements.

The Company has a non-exclusive worldwide license from the Baylor College of Medicine to make, have made, use and sell a panel of DNA probes for the diagnosis of fragile X. Royalties paid during fiscal 1992 are considered immaterial.

The Company has licensed from Cetus Corporation, on a non-exclusive and non-transferable basis, the patented technology to perform polymerase chain reactions. This license is for the life of the patents. The Company currently uses this technology to perform certain tests for detecting and diagnosing inherited diseases and cancers. Royalties paid during fiscal 1992 are not considered material.

There is an interference proceeding pending in the United States Patent and Trademark Office and other similar proceedings both in the European Patent Office and in the United Kingdom with regard to patent matters pertaining to rennin. Certain of these matters have been pending for some time. Depending upon the outcome, Collaborative's rights to rennin patent rights in the United Kingdom and in Europe, as well as in the United States, may be adversely affected.

The Company has not followed a policy of conducting infringement searches of patents relating to its research and development programs, but rather has allowed its licensees

and customers to determine if products or processes infringe any patent rights. Thus, there may be other patents unknown to the Company which may affect its rights to make, use and sell certain products and processes. The Company intends to undertake patent infringement searches in the future only in the event that such searches appear warranted, taking into consideration a variety of factors, including whether the Company intends to make, use or sell a product or process, the state of the art and the costs involved.

These licenses, exclusive and non-exclusive, have allowed access to certain technologies which the Company believes are significant in its development efforts or as product protection. The Company further believes that, in certain circumstances, licensing is a cost-effective alternative to internally-funded research and development.

(e) Marketing

The Company has a marketing and sales force to directly market its diagnostic testing services. These services are marketed worldwide to clinicians and researchers interested in genetic diseases, oncology, bone marrow transplantation and paternity.

Certain of the Company's products and processes under development have been licensed to third parties which have exclusive rights to market or further license certain of such products. Such exclusive rights may adversely affect the Company's ability to exploit commercially its technology. As new products or processes are developed, the Company will determine whether direct marketing, joint venture or licensing arrangements will lead to the fullest realization of the commercial potential of such products or processes. In making such a determination, the Company will consider such factors as the capital investment of the project, the aggregate research, development and marketing costs, the production requirements, the nature of the technology, the market size, the relative ease of market entry, required distribution channels and the extent to which the product appears to be subject to regulatory constraints on production and sale.

(f) Competition

Several other entities are engaged in research relating to the development of diagnostic tests for inherited diseases utilizing DNA probes which are similar to the Company's DNA technology. Other laboratories offer similar complements of tests; nevertheless, the Company believes that competition is based on reliability, service, turnaround time and customer education. To date, a number of such tests are in commercial use, and the Company expects that several additional tests will be developed in the near future. Some

of the Company's competitors may have greater financial, marketing and human resources than does the Company.

The Company believes that as the biotechnology industry continues to develop, the primary competitive factors will be the ability to develop advanced technology, to develop proprietary products or processes or obtain patent protection, to attract and retain skilled technical and managerial personnel, to commercialize and market technological improvements and to obtain funding for the equipment expenditures necessary for commercial manufacture.

Colleges, universities and public and private research organizations are also active in the field of biotechnology and recombinant DNA research, and they may seek patent protection of their inventions. Although several of these organizations compete with the Company in recruiting scientific personnel, they are not generally engaged in the direct commercialization of any products or processes which they develop.

(g) Government Regulation

Substantial segments of the Company's present and proposed operations may be subject to regulation by federal, state and local governmental authorities. Such regulations apply not only to the Company's research, development and manufacturing activities, but also to the marketing by the Company or its contract customers of existing and proposed products and processes, particularly those involving pharmaceutical applications, and to the Company's services offered through its Diagnostic Services Division.

Guidelines for the regulation of recombinant DNA research have been adopted by the City of Waltham, Massachusetts, where the Company's recombinant DNA research and development activities are currently conducted. Under the ordinance, which was passed by the Waltham City Council in 1981, a private company engaged in recombinant DNA research must agree to abide by guidelines promulgated by the National Institutes of Health ("NIH") for recombinant DNA research, and must provide Waltham with certain additional information. The Waltham ordinance prohibits experimentation with, or the use of, recombinant DNA technology which requires the highest level of containment under the NIH guidelines and also forbids the use of humans as experimental subjects for recombinant DNA research.

The Company's Diagnostic Reference Laboratory requires licenses from various state and federal agencies in order to be able to offer its services commercially and has obtained such licenses. In addition, the Company received Medicare Certification in July 1986 and Blue Cross/Blue Shield Provider Certification in October 1991; it is in the process

of obtaining Provider Certification from Medicaid. The Company may be subject to future changes in licensing requirements relating to these services.

The Company's present and future business will likely be subject also to varying degrees of additional regulation under the Atomic Energy Act, Occupational Safety and Health Act, Environmental Protection Act, Animal Welfare Act, Toxic Substances Control Act and other present or possible future local, state or federal regulation. The extent of adverse government regulation which might result from future legislation or administrative action cannot be accurately predicted.

(h) Human Resources

Employees As of August 31, 1992, the Company had 69 full-time employees, of whom 48 were engaged in research, development and production activities, and 21 in selling, general and administrative functions. Eighteen of the Company's employees hold Ph.D degrees and 23 other personnel hold advanced degrees.

The Company provides its employees with opportunities for internal and external interaction with scientific professionals through consultation with scientific advisory consultants, technical meetings and scientific collaborations and publications in leading scientific journals.

None of the Company's employees are covered by a collective bargaining agreement, and the Company considers its relations with its employees to be excellent. The Company believes that its compensation and other employee benefit plans are competitive, and key scientific and management personnel have been or will be offered an equity participation opportunity which the Company believes to be necessary to attract and retain such personnel.

Executive Officers of Registrant

The executive officers of the Company are as follows:

Name	Age	Position
Orrie M. Friedman	77	Chairman, Chief Executive Officer and President
Gerald F. Vovis	49	Senior Vice President -- Research and Development
William P. Johnson	48	Senior Vice President and General Manager -- Collaborative Diagnostics
Fenel M. Eloi	34	Vice President, Treasurer and Chief Financial Officer

All officers serve at the discretion of the Board of Directors.

Dr. Orrie M. Friedman, the founder of the Company, is Chairman of the Board of Directors, has been Chief Executive Officer since 1986 and reassumed the role of President in June 1989. Since the Company's incorporation in 1961, he was President and Scientific Director prior to July 1982, and from July 1982 to July 1986 he was Chairman of the Board. Prior to founding the Company, Dr. Friedman was Professor of Chemistry at Brandeis University and Assistant Professor at the Harvard Medical School. Dr. Friedman holds a Ph.D. in Chemistry from McGill University in Canada.

Dr. Gerald F. Vovis, Senior Vice President -- Research and Development, is responsible for all of Collaborative's scientific and technological activities involving its DNA technology, including grant and contract research. He has held positions of increasing responsibility since joining the Company in 1980. Before joining the Company, Dr. Vovis spent ten years in the Genetics Department of Rockefeller University in New York City as a Research Associate and Faculty member. He earned his Ph.D. in Biology from Case Western Reserve University in Ohio.

Mr. William P. Johnson, Senior Vice President and General Manager -- Collaborative Diagnostics, joined the Company in February 1989 as Vice President, Treasurer and Chief Financial Officer, and was promoted to his current position in October 1991. Prior to joining the Company, he was Chief Financial Officer for Elscint Inc. (the U.S. subsidiary of the Israeli parent company in the medical imaging industry). From 1980 to 1985 Mr. Johnson held

various Controller positions with Computervision Corporation in both domestic and international areas. Prior to 1980, he held various financial management positions with The Reece Corporation, Itek Corporation and Ernst & Young (an international public accounting firm). Mr. Johnson holds a B.S. in Accounting from Boston College and a Masters in Business Administration from Babson College.

Mr. Fenel M. Eloi, Vice President, Treasurer and Chief Financial Officer, joined the Company in September 1989 as Corporate Controller and was promoted to his current position in October 1991. Prior to joining the Company, Mr. Eloi held various financial management positions at GTE in their Communication Systems Sector. Prior to 1984, he held various financial positions, both domestic and international, with American Heamonetics and Simplex Time Recorder Co. Mr. Eloi holds a B.S. in Accounting from Lee College in Tennessee and a Masters in Business Administration from Anna Maria School of Business.

Item 2. PROPERTIES

The Company's research, development and Reference Laboratory activities are conducted in a facility located at 1365 Main Street, Waltham, Massachusetts. Recombinant DNA research is also conducted at that facility, where the Company has leased approximately 15,000 square feet of space under a lease expiring December 31, 1992 with the option for a five-year renewal. The Company's executive offices and Collaborative Diagnostics, our medical diagnostic testing division, have recently been relocated to a facility located at 100 Beaver Street, Waltham, Massachusetts, where the Company has leased approximately 23,000 square feet of space under a lease expiring August 1994 with the option for a one-year renewal.

During fiscal 1992, the Company incurred aggregate rental costs for all facilities of approximately $193,000. The low rental cost for the current fiscal year reflects the fact that for most of the year, the Company's executive offices were located at the Two Oak Park, Bedford, facility under a 2,000 square foot sublease agreement with Becton Dickinson and Company. The aggregate minimum rental to be paid in fiscal 1993 is expected to be approximately $313,000.

Item 3. LEGAL PROCEEDINGS

None.

Item 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

None.

PART II

Item 5. MARKET FOR THE REGISTRANT'S COMMON STOCK AND RELATED SECURITY HOLDER MATTERS

The Company's common stock is traded on the NASDAQ National Market System (ticker symbol "CRIC"). The table below sets forth the range of high and low quotations for each fiscal quarter of the Company during 1992 and 1991 as furnished by the National Association of Securities Dealers Quotation System.

	1992		1991	
	High	Low	High	Low
First quarter	3 1/8	1 1/2	1 3/4	1
Second quarter	3 1/2	1 3/8	1 5/8	3/4
Third quarter	3 3/16	1 3/4	2 1/4	1 1/4
Fourth quarter	2	1 3/8	1 7/8	7/8

In July 1987, the Massachusetts Legislature enacted a so-called "control share acquisition statute". In general, this statute would prevent anyone who acquires 20% or more of the outstanding shares of a publicly held, Massachusetts corporation from voting those shares unless "disinterested" shareholders vote to enfranchise the acquirer. The statute permits corporations to opt out of its coverage by amending their articles of organization or by-laws. On October 20, 1987, the Board of Directors approved such an amendment to the Company's Bylaws by adding the following provision as Section 8.3 thereof:

> "8.3. Control Share Acquisitions. The provisions of Massachusetts General Laws chapter 110D shall not apply to any control share acquisition of shares of the corporation."

In July 1989, the Massachusetts Legislature enacted a so-called "business combination statute". In general, this statute provides that, for three years after an acquirer has purchased at least 5% but less than 90% of the outstanding stock of a publicly held, Massachusetts corporation, a merger with the acquirer (and certain other transactions) cannot be effected unless the stock acquisition was approved in advance by the Board of Directors. As permitted by this statute, effective October 16, 1989, the Board of Directors approved an amendment to the Company's Bylaws by adding the following sentence to Section 2.8 thereof:

> "The provisions of Chapter 110F of the Massachusetts General Laws shall not apply to the Company."

In April 1990, the Massachusetts Legislature enacted a statute which mandated that most public companies incorporated in Massachusetts have a "staggered" or "classified" Board of Directors, unless a company opts out of the law. In general, this statute requires that, unless a company opts out, a Massachusetts corporation having a class of voting stock registered under the Securities Exchange Act of 1934 must have a staggered board with three classes serving three year terms. As permitted by the statute, effective October 15, 1990, the Board of Directors adopted a resolution exempting the Company from coverage under this statute.

As of November 19, 1992 there were approximately 1,704 shareholders of record of the Company's Common Stock.

The Company has not paid any dividends since its inception and presently anticipates that all earnings, if any, will be retained for development of the Company's business and that no dividends on its Common Stock will be declared in the foreseeable future. Any future dividends will be subject to the discretion of the Company's Board of Directors and will depend upon, among other things, future earnings, the operating and financial condition of the Company, its capital requirements and general business conditions.

Item 6. SELECTED CONSOLIDATED FINANCIAL DATA

For the Year Ended August 31,	1992	1991	1990	1989	1988
Product & Service Revenue	$ 792,225	$ 6,763,636	$ 6,819,129	$ 7,493,182	$10,503,833
Research Contract Revenue	4,210,053	2,193,245	2,139,570	3,927,280	4,356,084
Total Revenues	5,508,336	9,119,707	9,282,560	11,984,220	15,444,298
Net Loss	(2,078,711)	(1,687,095)	(2,627,263)	(4,110,515)	(863,097)
Per Share	(.19)	(.16)	(.25)	(.39)	(.08)
Average Common Shares	10,662,551	10,659,249	10,656,679	10,655,141	10,649,847
Total Working Capital	5,768,331	8,779,828	6,122,749	7,474,777	10,997,887
Total Assets	9,354,613	10,790,253	12,941,297	15,179,501	19,446,602
Shareholders' Equity	$ 6,918,774	$ 8,997,942	$10,549,580	$13,094,808	$17,111,376

No dividends on Common Stock have been declared or paid by the Company since its organization.

Item 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Overview

Revenue from all operating segments increased substantially during fiscal year 1992. Interest income was substantially higher in the current fiscal year. However, the sale of the Biomedical Products business in the prior fiscal year led to a decline in total revenues. Costs and expenses decreased both in absolute dollars and as a percentage of revenues. The operating loss, in comparison to the prior year, was substantially reduced; however, the net loss increased due to a non-recurring gain recorded in the prior year on the sale of the Biomedical Products business to Becton Dickinson.

Financial Condition

Cash and short-term investments at August 31, 1992 were approximately $7.1 million. The Company used approximately $1.5 million of its cash resources during fiscal 1992, primarily to support operations. Although the Company used approximately $2.3 million of its cash resources during fiscal 1991 to support operations, the sale of its Biomedical Products business generated $8.1 million of cash resulting in a net increase in cash of $5.6 million from fiscal 1990. During 1990, the Company used approximately $1.0 million of its cash resources.

Although operating revenues, excluding the Biomedical Products business, have doubled from the prior year, trade receivables increased slightly less than $.1 million reflecting the impact of negotiating advance payments with the NIH on grants. Overall, lower receivables reflect the successful collection of the retained receivable which resulted from the sale of the Biomedical Products business.

Expenditures for equipment were approximately $.2 million for each of 1992, 1991 and 1990.

The Company acquired a prenatal diagnostic laboratory on September 30, 1991 in furtherance of its goal of becoming a full service genetic testing laboratory. The final purchase price was $.9 million and required a cash outlay of approximately $.6 million and a short-term note payable of $.3 million.

As of August 31, 1991, the Company had debt obligations of $.4 million resulting from a capital lease agreement with BankBoston Leasing for the financing of certain equipment. The credit limit on that agreement is $1.0 million. The Company feels that its cash and short-term investments are adequate to support operational and capital requirements for the short term.

Results of Operations

Consolidated revenues declined approximately 40% from $9.1 million in 1991 to $5.5 million in 1992 due entirely to the loss of revenue from the Biomedical Products business which was sold in fiscal 1991. The net loss increased approximately $.4 million in fiscal 1992 to $2.1 million from $1.7 million in fiscal 1991 due entirely to a gain of $2.1 million recorded in fiscal 1991 on the sale of the Biomedical Products business. Fiscal 1990 also had a non-recurring gain of $.7 million resulting from the settlement with Sandoz AG.

Product and service revenue, excluding the Biomedical Products business, increased significantly to $.8 million in fiscal 1992 compared to $.4 million in fiscal 1991. The increase in revenue is due substantially to the acquisition of a cytogenetics laboratory on September 30, 1991. However, product and service revenue, including Biomedical Products, decreased 88% in fiscal 1992 from $6.8 million in fiscal 1991. Product and service revenue for fiscal 1990 was $6.8 million.

Royalty income increased substantially in fiscal 1992 to approximately $121,000 from $23,000 in fiscal 1991 reflecting the first royalty payment and accrual from Dow Chemical for the license of the rennin patent to Pfizer. The current year income reflects royalty on twenty four months of revenue due to the timing of notification of payments to be received.

Research contract revenue increased substantially from $2.2 million in fiscal 1991 to $4.2 million in fiscal 1992 due primarily to the award of several contracts from NIH in the current fiscal year.

Interest income increased substantially to $.4 million in fiscal 1992 from $.1 million in fiscal 1991 due primarily to higher average invested cash balances in the current fiscal year. Interest income for 1990 was $.3 million.

Costs and Expenses

Total costs and expenses decreased substantially by 41% to $7.6 million in fiscal 1992 from $12.9 million in fiscal 1991 due mostly to the sale of the Biomedical Products business. Total costs and expenses for fiscal 1990 were $12.6 million.

Costs of product and service revenue decreased approximately $3.1 million from $4.2 million in fiscal 1991 to $1.1 million in fiscal 1992 reflecting the reduction of approximately $3.6 million of product cost associated with the Biomedical Products business. That reduction was offset by approximately a $.5 million increase in cost associated with volume and investment in the growth of the diagnostic reference laboratory. Consequently, costs of product and

service revenue, as a percent of revenues, increased approximately 80% from fiscal 1991 reflecting the underutilization of the current laboratory capacity. Costs of product sales in 1990 were $4.1 million.

Costs of research contract revenue were $3.6 million in fiscal 1992 compared to $2.1 million in 1991 reflecting the increase in volume. As a percent of revenue, these costs decreased approximately 9% from the prior year reflecting the absorption of all direct cost associated with that business and its marginal contribution to G&A expenses. In fiscal 1990, costs of research contract revenue were $2.0 million.

Company-funded research and development expenses decreased substantially, approximately $2.0 million from $2.3 million in fiscal 1991 to $.3 million in fiscal 1992. This decrease reflects increased overhead absorption by the research contract business as a result of increased volume. These overhead costs were, in prior years, subsidized by the Company. The substantial decrease was offset by a slight increase in process development activities in support of the diagnostic testing business. Research and development expenses for fiscal 1990 were $2.0 million.

Selling, general and administrative expenses decreased substantially, approximately $1.8 million from $4.3 million in fiscal 1991 to $2.5 million in fiscal 1992. This decrease reflects the reduction of selling expenses associated with the Biomedical Products business and a reduction in headcount in G&A commensurate with the reduction in sales volume. Selling, general and administrative expenses in 1990 were $4.6 million.

Gain on Sale of Biomedical Products Business

On August 30, 1991, the Company sold the assets of its Biomedical Products business to Becton Dickinson and Company for $9.0 million plus a potential earnout in the form of royalties up to a maximum of $1.6 million over the next five years. This transaction resulted in a non-recurring gain of $2.6 million offset by $.5 million of expenses pertaining to the transaction leaving a net gain of $2.1 million which reduced the net loss for the year.

Gain from Settlement of Sandoz Contract

During fiscal 1990, the Company reached a settlement with Sandoz AG regarding the development contract for prourokinase which resulted in a non-recurring gain of $655,000 and contributed to the reduction in the net loss for fiscal 1990.

Item 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

Financial statements and supplementary data required by Item 8 are set forth at the pages indicated in Item 14(a) below.

Item 9. DISAGREEMENTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

PART III

Pursuant to General Instruction G(3) to Form 10-K, the information required for Part III (Items 10, 11, 12 and 13) is incorporated herein by reference from the Company's proxy statement for the Special Meeting of Shareholders in Lieu of an Annual Meeting to be held on January 25, 1993. The information required by Item 10, relating to Executive Officers, has been furnished in Part I of this report entitled "Executive Officers of the Registrant", pursuant to Instruction 3 of Item 401(b) of Regulation S-K.

PART IV

Item 14. EXHIBITS, FINANCIAL STATEMENT SCHEDULES AND REPORTS ON FORM 8-K

(a) Financial Statements and Financial Statement Schedules (1) and (2). See "Index to Consolidated Financial Statements and Financial Statement Schedules" appearing on page 25.

(2)(3) EXHIBITS:

EXHIBIT INDEX

3.	--	Restated Articles of Organization and By-laws (1)
3.1	--	Amendment dated January 5, 1982 to Restated Articles of Organization (2)
3.2	--	Amendment dated January 24, 1983 to Restated Articles of Organization (3)
3.3	--	Amendment dated January 17, 1984 to Restated Articles of Organization (6)
3.4	--	Amendment dated October 20, 1987 to the By-laws (10)
3.5	--	Amendment dated December 9, 1987 to Restated Articles of Organization (11)
3.6	--	Amendment dated October 16, 1989 to the By-laws (13)
4.	--	Series B Restricted Stock Purchase Plan (3)
10.1	--	Research Agreement with The Dow Chemical Company dated May 21, 1980 (1)
10.2	--	Research Agreement with The Dow Chemical Company dated August 19, 1981 (1)
10.3	--	1981 Amended Stock Option Plan and Form of Stock Option Certificate (1)
10.4	--	Incentive Stock Option Plan and Form of Stock Option Certificate (1)
10.16	--	1984 Stock Option Plan and Form of Stock Option Certificate (7)
10.17	--	Collaborative Research Incentive Savings Plan (8)
10.17.1	--	Amendment dated November 4, 1986 to the Collaborative Research Incentive Savings Plan dated March 1, 1985 (9)
10.18	--	Lease dated December 20, 1985 relating to certain property in Bedford, Massachusetts (9)

10.21	--	Stock Option Agreement with Mr. Lawrence Levy (10)
10.22	--	Consulting Agreement with Mr. Lawrence Levy (10)
10.23	--	Form of Amendment to the 1981 Incentive Stock Option Plan (10)
10.26	--	Stock Option Agreement with Mr. Mark Friedman (12)
10.27	--	1988 Stock Option Plan and Form of Stock Option Certificate (12)
10.29	--	Letter Agreement with Dr. Rothchild (13)
10.30	--	Stock Option Agreement with Dr. Rothchild (13)
10.31	--	Agreement with Health Sciences Research Institute (Hoken Kagaku Kenkyojyo) (14)
10.32	--	1991 Stock Option Plan and Form of Stock Option Certificate (15)
22.	--	Subsidiaries of the Registrant (15)
24.	--	Consent of Independent Public Accountants (15)

FOOTNOTES

(1) Filed as exhibits to the Company's Registration Statement on Form S-1 (No. 2-75230) and incorporated herein by reference.

(2) Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended February 27, 1982 and incorporated herein by reference.

(3) Filed as exhibits to the Company's Quarterly Report on Form 10-Q for the quarter ended February 26, 1983 and incorporated herein by reference.

(4) Filed as exhibits to the Company's Annual Report on Form 10-K for the fiscal year ended August 31, 1982 and incorporated herein by reference.

(5) Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended November 26, 1984 and incorporated herein by reference.

(6) Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended February 25, 1984 and incorporated herein by reference.

(7) Filed as exhibits to the Company's Annual Report on Form 10-K for the fiscal year ended August 31, 1984 and incorporated herein by reference.

(8) Filed as exhibits to the Company's Annual Report on Form 10-K for the fiscal year ended August 31, 1985 and incorporated herein by reference.

(9) Filed as exhibits to the Company's Annual Report on Form 10-K for the fiscal year ended August 31, 1986 and incorporated herein by reference.

(10) Filed as exhibits to the Company's Annual Report on Form 10-K for the fiscal year ended August 31, 1987 and incorporated herein by reference.

(11) Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended November 28, 1987 and incorporated herein by reference.

(12) Filed as an exhibit to the Company's Annual Report on Form 10-K for the fiscal year ended August 31, 1988 and incorporated herein by reference.

(13) Filed as an exhibit to the Company's Annual Report on Form 10-K for the fiscal year ended August 31, 1989 and incorporated herein by reference.

(14) Filed as an exhibit to the Company's Annual Report on Form 10-K for the fiscal year ended August 31, 1990 and incorporated herein by reference.

(15) Filed herewith.

(b) Reports on Form 8-K

No reports were filed on Form 8-K during the quarter ended August 31, 1991.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, Collaborative Research, Inc. has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, on November 23, 1992.

COLLABORATIVE RESEARCH, INC.

By _____ORRIE M. FRIEDMAN_____
Orrie M. Friedman
Chief Executive Officer

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities indicated as of November 23, 1992.

Signature	Title
_____ORRIE M. FRIEDMAN_____ Orrie M. Friedman	Chairman of the Board; Chief Executive Officer; President; and Director (Principal Executive Officer)
_____MARK D. FRIEDMAN_____ Mark D. Friedman	Director
_____LAWRENCE LEVY_____ Lawrence Levy	Director
_____SEYMOUR ROTHCHILD_____ Seymour Rothchild	Director
_____PAUL C. ZAMECNIK_____ Paul C. Zamecnik	Director
_____FENEL M. ELOI_____ Fenel M. Eloi	Vice President; Treasurer; and Chief Financial Officer (Principal Financial and Accounting Officer)

COLLABORATIVE RESEARCH, INC. AND SUBSIDIARIES

Index to Consolidated Financial Statements and Financial Statement Schedules

Schedules not included herein are omitted for the reason that they are not applicable or that the required information appears in the Consolidated Financial Statements or Notes thereto.

Consolidated Balance Sheets

August 31, 1992 and 1991	1992	1991
Assets:		
Current Assets:		
Cash and Cash Equivalents (Note 1)	$ 7,144,140	$ 8,680,913
Short-term Investments (Note 1)	0	360,000
Receivables:		
Trade and Other (less allowances for doubtful accounts of $74,000 in 1992 and $16,000 in 1991)	389,066	846,325
Unbilled Costs (Note 1)	168,040	341,949
Prepaid Expenses	65,251	231,564
Total Current Assets	7,766,497	10,460,751
Equipment and Leasehold Improvements, at Cost (Notes 1 and 6):		
Laboratory and Scientific Equipment	675,505	670,475
Leasehold Improvements	1,363,303	1,285,651
Office Equipment and Furniture	468,444	171,032
Unfinished Plant and Equipment	148,663	0
	2,655,915	2,127,158
Less Accumulated Depreciation and Amortization	1,870,977	1,797,656
	784,938	329,502
Goodwill (net of accumulated amortization of $38,580)(Note 9)	803,178	0
Total Assets	$ 9,354,613	$10,790,253
Liabilities and Shareholders' Equity:		
Current Liabilities:		
Accounts Payable	$ 402,007	$ 501,517
Accrued Expenses (Note 8)	785,835	1,070,869
Short-term Note Payable (Note 9)	268,500	0
Deferred Contract Revenue	393,817	108,537
Current Maturities of Capital Lease Obligation (Note 6)	148,007	0
Total Current Liabilities	1,998,166	1,680,923
Deferred Compensation (Note 7)	162,537	111,388
Capital Lease Obligation, Net of Current Maturities (Note 6)	275,136	0
Commitments and Contingencies (Note 5)		
Shareholders' Equity (Notes 1 and 7):		
Common Stock, $.10 Par Value -- Authorized -- 17,500,000 shares; Issued and Outstanding -- 10,664,166 shares in 1992 and 10,661,541 shares in 1991	1,066,416	1,066,154
Series B Restricted Stock, $.10 Par Value - Issued and Outstanding -- 57,512 shares in 1992 and 1991	5,751	5,751
Additional Paid-in Capital	37,122,427	37,123,146
Accumulated Deficit	(31,198,854)	(29,120,143)
Installment Receivable from Sale of Series B Restricted Stock	(76,966)	(76,966)
Total Shareholders' Equity	6,918,774	8,997,942
Total Liabilities and Shareholders' Equity	$ 9,354,613	$10,790,253

The accompanying notes are an integral part of these consolidated financial statements.

Consolidated Statements of Operations

For the Years Ended August 31, 1992, 1991 and 1990	1992	1991	1990
Revenues:			
Biomedical Product Revenue (Note 2)	$ 0	$ 6,412,078	$ 6,347,749
Product & Service Revenue (Note 1)	792,225	351,558	471,380
Research Contract Revenue (Note 1)	4,210,053	2,193,245	2,139,570
Royalties (Note 1)	121,348	22,720	7,539
Interest Income	384,710	140,106	316,322
Total Revenues	5,508,336	9,119,707	9,282,560
Costs and Expenses:			
Cost of Product & Service Revenue	1,132,432	4,250,975	4,054,327
Cost of Research Contract Revenue	3,601,781	2,093,911	1,974,829
Research and Development	359,529	2,300,650	1,956,423
Selling, General and Administrative	2,493,305	4,265,266	4,579,679
Total Costs and Expenses	7,587,047	12,910,802	12,565,258
Operating Loss	(2,078,711)	(3,791,095)	(3,282,698)
Non-recurring Gains (Notes 2 and 3)	0	2,104,000	655,435
Net Loss	$(2,078,711)	$(1,687,095)	$(2,627,263)
Net Loss per Common Share (Note 1)	$ (.19)	$ (.16)	$ (.25)
Weighted Average Common Shares Outstanding	10,662,551	10,659,249	10,656,679

The accompanying notes are an integral part of these consolidated financial statements.

Consolidated Statements of Shareholders' Equity

For the Years Ended August 31, 1990, 1991 and 1992	Common Stock Shares	Common Stock Amount	Series B Restricted Stock Shares	Series B Restricted Stock Amount	Additional Paid-in Capital	Accumulated Deficit	Installment Receivable from Sale of Stock (Note 7)	Total Shareholders' Equity
Balance at August 31, 1989	10,655,141	$1,065,514	57,512	$5,751	$36,906,294	$(24,805,785)	$(76,966)	$13,094,808
Exercise of Stock Options	2,500	250			17,063			17,313
Cancellation/Termination of Stock Options					64,722			64,722
Net Loss						(2,627,263)		(2,627,263)
Balance at August 31, 1990	10,657,641	1,065,764	57,512	5,751	36,988,079	(27,433,048)	(76,966)	10,549,580
Exercise of Stock Options	3,900	390			27,413			27,803
Cancellation/Termination of Stock Options					107,654			107,654
Net Loss						(1,687,095)		(1,687,095)
Balance at August 31, 1991	10,661,541	1,066,154	57,512	5,751	37,123,146	(29,120,143)	(76,966)	8,997,942
Exercise of Stock Options	2,625	262			6,042			6,304
Cancellation/Termination of Stock Options					(6,761)			(6,761)
Net Loss						(2,078,711)		(2,078,711)
Balance at August 31, 1992	10,664,166	$1,066,416	57,512	$5,751	$37,122,427	$(31,198,854)	$(76,966)	$ 6,918,774

The accompanying notes are an integral part of these consolidated financial statements.

Consolidated Statements of Cash Flows

For the Years Ended August 31, 1992, 1991 and 1990	1992	1991	1990
Cash Flows from Operating Activities:			
Net Loss	$(2,078,711)	$(1,687,095)	$(2,627,263)
Adjustments to Reconcile Net Loss to Net Cash Used by Operating Activities:			
Gain on Sale of Net Assets	(12,217)	(2,104,000)	0
Gain on Contract Settlement	0	0	(515,435)
Depreciation and Amortization	212,321	1,460,979	1,755,022
Loss on Sale of Equipment	0	0	25,321
Deferred Compensation	44,387	18,313	29,760
Provisions for Accounts Receivable and Inventory Reserves	69,801	176,345	141,419
Changes in Assets and Liabilities:			
(Increase) Decrease in Current Assets:			
Short-term Investments	360,000	75,000	(75,000)
Receivables	(138,633)	(316,779)	(15,978)
Inventories	0	136,135	123,038
Prepaid Expenses	(8,687)	(220,128)	648
Increase (Decrease) in Current Liabilities:			
Accounts Payable	(99,510)	306,960	979
Bank Overdraft	0	(391,792)	160,262
Accrued Expenses	(460,279)	488,215	(197,582)
Deferred Contract Revenue	285,280	(210,545)	262,140
Total Adjustments	252,463	(581,297)	1,694,594
Net Cash Used by Operating Activities	(1,826,248)	(2,268,392)	(932,669)
Cash Flows from Investing Activities:			
Purchase of Equipment and Leasehold Improvements	(167,319)	(229,518)	(152,457)
Proceeds from Sale of Net Assets	969,000	8,100,000	0
Payments for Net Assets Acquired	(488,485)	0	0
Net Cash Provided by (Used for) Investing Activities	313,196	7,870,482	(152,457)
Cash Flows from Financing Activities:			
Proceeds from Sale of Stock	6,305	780	500
Principal Payments Under Capital Lease Obligation	(30,026)	(39,219)	(3,087)
Net Cash Used by Financing Activities	(23,721)	(38,439)	(2,587)
Net Increase (Decrease) in Cash and Cash Equivalents	(1,536,773)	5,563,651	(1,087,713)
Cash and Cash Equivalents at Beginning of Year	8,680,913	3,117,262	4,204,975
Cash and Cash Equivalents at End of Year	$ 7,144,140	$ 8,680,913	$ 3,117,262

The accompanying notes are an integral part of these consolidated financial statements.

1. Summary of Significant Accounting Policies:

Consolidation
The accompanying consolidated financial statements include the accounts of the Company and its subsidiaries. All material intercompany balances and transactions have been eliminated in consolidation.

Research and Development Contract Accounting
The Company participates in both fixed price and cost plus fixed fee contracts. Cost plus contracts have no stated deliverables associated with them. The Company is, however, required to prepare a scientific report of the Company's research and the results thereof. Revenues under cost plus and fixed price contracts are recognized in the proportion that costs incurred bear to total estimated costs. At the Company's option, cost may exceed the amounts funded by these contracts, and the excess is charged to expense. Unbilled costs represent the excess of total expenditures on contracts, plus earned fees thereon, over billings.

Cash Equivalents and Short-term Investments
Cash equivalents and short-term investments consisting of certificates of deposit, treasury notes and money market funds are valued at cost which approximates market value. As of August 31, 1992, the Company has restricted cash of approximately $150,000.

Statement of Cash Flows
The Company considers cash in bank and liquid debt instruments purchased with an original maturity of three months or less to be cash equivalents. Interest and income taxes paid are immaterial in each of the three years ended August 31, 1992. For the year ended August 31, 1992, a capital lease obligation of $453,169 was incurred when the Company entered into a lease agreement for new office and laboratory equipment. For the year ended August 31, 1990, a capital lease obligation of $136,087 was incurred when the Company entered into a lease agreement for new equipment. That lease obligation was transferred to Becton Dickinson on August 30, 1991. (See Note 2.)

Equipment and Leasehold Improvements
Equipment and leasehold improvements are depreciated over their estimated useful lives using the straight-line method. The estimated useful life for leasehold improvements is the initial term of the lease plus an extension option period. Equipment and all other depreciable assets' useful lives vary from

three to ten years. Expenditures for maintenance and repairs are expensed as incurred.

Service Revenue
Revenues are recognized in the period in which services are rendered. Revenues subject to Medicare or third-party reimbursement are recorded at estimated reimbursable amounts.

Royalty Revenue
Royalty revenue is recorded as earned. Royalties represent receipts from The Dow Chemical Company and CIBA-Corning for license agreements for rennin and EMIA, respectively.

Net Loss per Common Share
Net loss per common share has been computed based upon the weighted average number of common shares outstanding during each period. Common share equivalents consisting of outstanding stock options have not been used to compute the loss per common share as their effect would be antidilutive.

Reclassifications
Certain amounts previously reported in the consolidated financial statements have been reclassified to conform with the 1992 presentation. Such reclassifications have no effect on previously reported results.

2. Gain on Sale of Biomedical Products Business:
On August 30, 1991, the Company sold the net assets of its Biomedical Products business to Becton Dickinson and Company for $9.0 million, plus a potential earnout in the form of royalties up to a maximum of $1.6 million over the next four years. The transaction resulted in a non-recurring gain of $2.7 million offset by $.6 million of related expenses, resulting in a net gain of $2.1 million which was recorded in fiscal 1991.

3. Gain from Settlement of Sandoz Contract:
In fiscal 1990, the Company reached a settlement with Sandoz AG on a contract which was terminated on August 31, 1989. The settlement resulted in a gain of $655,000.

4. Income Taxes:
At August 31, 1992, the Company has available federal net operating loss carryforwards, subject to Internal Revenue Service review, of approximately $32,267,000 to offset against future taxable income, expiring at various dates through 2007. In addition, the Company had investment tax credits and research and experimentation credits of approximately $1,083,000 available to offset future federal income tax liabilities, expiring at various dates through 2001.

The Financial Accounting Standards Board has issued pronouncements that would require the Company to change its

method of accounting for income taxes beginning no later than fiscal 1993. Because the Company has significant net operating loss carryforwards, implementation of the pronouncements is not expected to have a material effect on the Company's reported financial position and results of operations.

5. Commitments and Contingencies:
At August 31, 1992, the Company has operating leases for office space and laboratory facilities which require minimum lease payments during each of the following years:

1993	$ 313,285
1994	313,285
1995	313,285
1996	52,000
1997	52,000
	$1,043,855

Rental expense charged to operations was approximately $193,000 in 1992, $518,000 in 1991 and $510,000 in 1990, not including operating expenses.

There is an interference proceeding pending in the United States Patent and Trademark Office and other similar proceedings both in the European Patent Office and in the United Kingdom with regard to patent matters pertaining to rennin. Depending upon the outcome, the Company's rights to rennin patent rights in the United Kingdom and in Europe, as well as in the United States, may be adversely affected. Management is presently unable to predict the likely outcome of these proceedings, but believes that these proceedings will not have a material adverse affect on the consolidated financial statements as of August 31, 1992.

6. Capital Lease Obligations:
The Company leases certain office and laboratory equipment under capital lease agreements. The net book value of this equipment was approximately $396,000 at August 31, 1992. Future minimum lease payments under the capital leases, together with the present value of the net minimum lease payments at August 31, 1992, are as follows:

1993	$173,822
1994	173,822
1995	119,471
Total minimum lease payments	467,115
Less-Amount representing interest	43,972
Present value of total minimum lease payments	423,143
Less-Current portion	148,007
	$275,136

7. Shareholders' Equity:

Series B Restricted Stock
On January 21, 1983, the shareholders approved an amendment to the Restated Articles of Organization of the Company designating 625,000 shares of common stock as Series B Restricted Stock ("Series B Stock") and adopted a Series B Restricted Stock Purchase Plan (the "Plan"). The Plan terminated August 31, 1986, and 57,512 shares remain outstanding. In the event of liquidation, holders of common stock are entitled to receive, prior to and in preference to any distribution of the Company's assets to the holders of Series B Stock, the greater of: (a) $5.00 per share; or (b) an amount per share equal to ten (10) times the amount which, after such distribution, would remain available for distribution to holders of the Series B Stock. After such preferential distribution, the remaining assets, if any, of the Company would be distributed ratably to the holders of common stock and Series B Stock.

Common Stock Options
The Company has various stock option plans and agreements as described below.

The Company adopted an incentive stock option plan (the "Incentive Plan") in October 1981, pursuant to which 250,000 shares were reserved for issuance to key employees. No further options may be granted under this plan.

In August 1981, the Company adopted a stock option plan, as amended in October 1981 (the "1981 Plan"), pursuant to which 500,000 shares of common stock were reserved for issuance to key employees. In May 1984, the number of reserved shares was reduced to 300,000. No further options may be granted under the 1981 Plan.

In 1984, the Company adopted the 1984 Stock Option Plan (the "1984 Plan"), pursuant to which 500,000 shares were reserved for issuance to key employees and consultants. The options may be granted at prices not less than 50% of the fair market value of the common stock on the date of grant.

In 1988, the Company adopted a stock option plan (the

"1988 Plan"), under which 750,000 shares were reserved for issuance to key employees and consultants. The options may be granted at prices not less than 50% of the fair market value of the common stock on the date of grant. Under separate agreements ("Other Stock Option Agreements"), the Company has granted directors and certain consultants of the Company options to purchase common stock.

In 1992, the Company adopted a stock option plan (the "1991 Plan"), under which 500,000 shares were reserved for issuance to key employees and consultants. No incentive stock option may be granted with a per share exercise price less than the fair market value per share at the date of grant. Non-incentive stock options may be granted at such price as may be determined by the Stock Option Committee, but not less than the par value of the common stock.

Fair market value is determined by computing the average value per share between the closing bid and asked price on the date of grant. The Company accounts for the compensation arising from the grant of stock options under certain plans as follows: a) at the date of grant, the Company establishes both a prepaid asset and a deferred compensation liability for the difference between the option price and fair market value; b) the Company amortizes the prepaid compensation to expense over the vesting period of the related options; and c) on the date of exercise, the Company removes the deferred compensation liability from its balance sheet and credits the appropriate equity accounts. For presentation purposes, the prepaid compensation is netted against the deferred compensation and the net amount is reflected as a deferred compensation liability on the balance sheet.

The compensation expense charged to operations was approximately $46,000, $18,000 and $30,000 during 1992, 1991 and 1990, respectively. Deferred compensation to be charged to future operations in the year in which these options become exercisable will be approximately $50,000, $47,000, $47,000 and $12,000 for 1993, 1994, 1995 and 1996, respectively.

The remaining outstanding options become exercisable through August 1996. There were 806,729 common shares available for future grants at August 31, 1992 under existing stock option plans. Plan data are summarized as follows:

	1992	1991	1990
Option shares:			
Granted	323,000	165,875	597,000
Exercised	(2,625)	(3,900)	(2,500)
Cancelled	(107,225)	(135,424)	(369,862)
Outstanding August 31	1,117,614	904,464	877,913
Price range of outstanding options at end of period	$.20-$11.94	$.20-$11.94	$.20-$11.94
Price range of exercised options during period	$.88-$1.38	$.20	$.20

8. Accrued Expenses:
The components of accrued expenses at the respective dates are as follows:

August 31,	1992	1991
Payroll and related expenses	$ 170,955	$ 232,368
Vacation accrual	110,188	74,478
Professional fees	38,559	221,538
Severance	25,000	120,000
Facilities relocation	79,039	112,703
Equipment lease accrual	131,610	0
All other	230,484	309,782
	$ 785,835	$1,070,869

9. Acquisition:
On September 30, 1991, the Company acquired the Prenatal Diagnostic Laboratory of the Eunice Kennedy Shriver Center for Mental Retardation, Inc., located in Waltham, Massachusetts, for a final purchase price of $.9 million consisting of $.6 million in cash and a note payable of $.3 million. The note payable, which is non-interest bearing, matures in the first quarter of fiscal 1993. The acquisition has been accounted for as a purchase. The purchase price has been allocated to the net assets acquired (equipment and furniture) based on their estimated fair market value, which was approximately $90,000. The remainder of the purchase price was allocated to goodwill which is being amortized over twenty years.

10. Incentive Savings Plan (401K):
The Collaborative Research Incentive Savings Plan (the "Plan") is maintained for the benefit of all employees. The Plan became effective March 1, 1985 and allows employees with one full year of service to make certain tax deferred voluntary contributions which the Company matches at the rate of 50% for the first 2% of salary and 25% for the next 4% of salary, limited to the first $50,000 of annual salary. On November 4, 1986, the Company granted to each active employee one hundred (100) shares, or a pro rated amount, of its common stock. Vesting occurred immediately for those employees with ten (10) or more years of service, and all others on May 4, 1987. The Company contributed $19,051, $34,506 and $33,583 to the Plan for 1992, 1991 and 1990, respectively.

11. Executive Bonus Plan:
In fiscal 1990, the Company adopted an Executive Bonus Plan pursuant to which certain executives may receive a bonus equal to varying percentages of their respective base salaries depending upon the Company's adjusted cash flow for the fiscal year. No amounts related to the Plan were charged to operations in 1992, 1991 and 1990.

SCHEDULE I

COLLABORATIVE RESEARCH, INC. AND SUBSIDIARIES
MARKETABLE SECURITIES AND OTHER INVESTMENTS

	Cost	Market Value at Balance Sheet Date	Amount at Which Each Issue is Carried on the Balance Sheet
August 31, 1991:			
Certificates of Deposit	$360,000	$360,000	$360,000

SCHEDULE VIII

COLLABORATIVE RESEARCH, INC. AND SUBSIDIARIES
VALUATION AND QUALIFYING ACCOUNTS
FOR THE YEARS ENDED AUGUST 31, 1992, 1991 AND 1990
RESERVE FOR DOUBTFUL ACCOUNTS

Balance, August 31, 1989	$ 99,041
Additions charged to expense	8,000
Write-off of uncollectible accounts, net	(84,496)
Balance, August 31, 1990	$ 22,545
Additions charged to expense	121,545
Write-off of uncollectible accounts, net	(128,466)
Balance, August 31, 1991	$ 15,624
Additions charged to expense	69,801
Write-off of uncollectible accounts, net	(11,035)
Balance, August 31, 1992	$ 74,390

SCHEDULE X

COLLABORATIVE RESEARCH, INC. AND SUBSIDIARIES
SUPPLEMENTARY INCOME STATEMENT INFORMATION
FOR THE YEARS ENDED AUGUST 31, 1992, 1991 AND 1990

	1992	1991	1990
Maintenance and repairs	$ 58,917	$ 73,417	$ 77,062
Advertising costs	$ 59,956	$346,157	$279,583

EXHIBIT 22

SUBSIDIARIES OF THE REGISTRANT

Collaborative Research, Inc. has three wholly-owned subsidiaries, two of which are Massachusetts corporations -- Collaborative Genetics, Inc. and Collaborative Securities Corporation -- and the third is a Delaware corporation -- Collaborative Diagnostic Services, Inc.

EXHIBIT 24

Arthur Andersen & Co.
One International Place
Boston MA 02110-2600

CONSENT OF INDEPENDENT PUBLIC ACCOUNTANTS

As independent public accountants, we hereby consent to the incorporation of our reports included in this Form 10-K, into the Company's previously filed Form S-8 Registration Statements No. 2-77846, No. 2-81123, No. 2-95446, No. 33-12633, No. 33-27885 and No. 33-45432.

Arthur Andersen & Co.
ARTHUR ANDERSEN & CO.

November 23, 1992

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-Q

QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d)
OF THE SECURITIES AND EXCHANGE ACT OF 1934

For Quarter Ended: May 29, 1993

Commission File No: 0-10824

COLLABORATIVE RESEARCH, INC.
(Exact name of registrant as specified in its charter)

MASSACHUSETTS	04-2297484
(State or other jurisdiction of incorporation or organization)	**(I.R.S. employer identification no.)**

100 BEAVER STREET, WALTHAM, MASSACHUSETTS	02154
(Address of principal executive offices)	**(Zip code)**

Registrant's telephone number: (617)487-7979

204 SECOND AVENUE, WALTHAM, MASSACHUSETTS 02154
(Former address of principal executive offices)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes _X_ No___

Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practicable date.

COMMON STOCK $.10 PAR VALUE	10,693,166 Outstanding July 9, 1993
SERIES B RESTRICTED STOCK $.10 PAR VALUE	57,512 Outstanding July 9, 1993

Collaborative Research, Inc. and Subsidiaries

Index to Financial Information (Unaudited) and Other Information

COLLABORATIVE RESEARCH, INC. AND SUBSIDIARIES
CONSOLIDATED CONDENSED STATEMENTS OF OPERATIONS (UNAUDITED)

	Thirteen Weeks Ended		Thirty-nine Weeks Ended	
	May 29, 1993	May 30, 1992	May 29, 1993	May 30, 1992
Revenues:				
Operating Revenue	$1,757,818	$1,414,749	$4,451,720	$3,562,527
Interest Income	33,500	108,853	139,980	285,199
Royalties	48,047	54,682	98,045	54,682
Total Revenues	1,839,365	1,578,284	4,689,745	3,902,408
Costs and Expenses:				
Cost of Revenue	1,722,764	1,219,130	4,723,672	3,346,675
Research and Development	22,200	82,098	195,887	234,568
Selling, General and Administrative	805,811	701,956	2,220,964	1,810,479
Total Costs and Expenses	2,550,775	2,003,184	7,140,523	5,391,722
Net Loss	($711,410)	($424,900)	($2,450,778)	($1,489,314)
Net Loss per Common Share	($0.07)	($0.04)	($0.23)	($0.14)
Weighted Average Number of Common Shares Outstanding	10,664,166	10,662,854	10,664,166	10,662,066

See notes to Consolidated Condensed Financial Statements.

COLLABORATIVE RESEARCH, INC. AND SUBSIDIARIES
CONSOLIDATED CONDENSED BALANCE SHEETS

	May 29, 1993 (Unaudited)	August 31, 1992
Assets:		
Current Assets:		
Cash and Cash Equivalents (Note 3)	$1,682,584	$7,144,140
Marketable Securities (Note 3)	2,000,000	0
Receivables:		
Trade and Other (net of allowances for doubtful accounts)	404,635	389,066
Unbilled Costs	192,995	168,040
Interest	33,513	0
Prepaid Expenses	137,771	65,251
Total Current Assets	4,451,498	7,766,497
Equipment and Leasehold Improvements, at Cost:		
Laboratory and Scientific Equipment	899,764	675,505
Leasehold Improvements	1,461,944	1,363,303
Office Equipment and Furniture	605,888	468,444
Unfinished Plant and Equipment	322	148,663
	2,967,918	2,655,915
Less Accumulated Depreciation and Amortization	2,101,667	1,870,977
	866,251	784,938
Goodwill (net of accumulated amortization) (Note 4)	771,612	803,178
Total Assets	$6,089,361	$9,354,613
Liabilities and Shareholders' Equity:		
Accounts Payable	$194,216	$402,007
Accrued Expenses	645,573	785,835
Short-term Notes Payable (Note 4)	0	268,500
Deferred Contract Revenue	36,884	393,817
Current Maturities of Capital Lease Obligation	284,455	148,007
Total Current Liabilities	1,161,128	1,998,166
Deferred Compensation	200,961	162,537
Capital Lease Obligation	259,276	275,136
Shareholders' Equity	4,467,996	6,918,774
Total Liabilities and Shareholders' Equity	$6,089,361	$9,354,613

See notes to Consolidated Condensed Financial Statements.

COLLABORATIVE RESEARCH, INC. AND SUBSIDIARIES
CONSOLIDATED STATEMENT OF CASH FLOWS (UNAUDITED)

	Thirty Nine Weeks Ended May 29, 1993	May 30, 1992
Cash Flows from Operating Activities:		
Net Loss	($2,450,778)	($1,489,314)
Adjustments to Reconcile Net Loss to Net Cash Used by Operating Activities:		
Gain on Sale of Net Assets	0	(12,217)
Depreciation & Amortization	264,160	148,877
Deferred Compensation	38,424	39,490
Provision for Accounts Receivable	67,659	57,294
Changes in Assets and Liabilities:		
(Increase) Decrease in Current Assets:		
Marketable Securities	(2,000,000)	0
Receivables	(141,696)	(176,719)
Prepaid Expenses	(72,520)	(41,962)
Increase (Decrease) in Current Liabilities:		
Accounts Payable	(207,791)	(253,974)
Accrued Expenses	(8,652)	(684,603)
Deferred Contract Revenue	(356,933)	10,946
Total Adjustments	(2,417,349)	(912,868)
Net Cash Used by Operating Activities	(4,868,127)	(2,402,182)
Cash Flows from Investment Activities:		
Purchase of Equipment and Leasehold Improvements	(129,213)	(204,348)
Payments for Net Assets Acquired	(268,500)	(488,483)
Proceeds from Sale of Net Assets	0	946,000
Net Cash(Used)/Provided by Investing Activities	(397,713)	253,169
Cash Flows from Financing Activities:		
Proceeds from Sale of Stock	0	263
Principal Payments under Capital Lease Obligation	(195,716)	0
Proceeds from Capital Lease Obligation	0	286,748
Net Cash Provided/(Used for) Financing Activities	(195,716)	287,011
Net Decrease in Cash and Cash Equivalents	(5,461,556)	(1,862,002)
Cash and Cash Equivalents at Beginning of Period	7,144,140	8,680,913
Cash and Cash Equivalents at End of Period	$1,682,584	$6,818,911

See notes to Consolidated Condensed Financial Statements.

Notes to Consolidated Condensed Financial Statements
(Unaudited)

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1. In the opinion of management, the accompanying unaudited consolidated condensed financial statements contain all adjustments necessary to present fairly the financial position of the Company as of May 29, 1993 and the results of its operations for the thirteen (13) and thirty-nine (39) week periods then ended. It is suggested that these consolidated condensed financial statements be read in conjunction with the consolidated financial statements and the notes thereto included in the Company's Annual Report to Shareholders for the year ended August 31, 1992.

   The results of operations for the thirteen (13) and thirty-nine (39) week periods ended May 29,1993 are not necessarily indicative of the results to be expected for the full year.

2. For all periods presented, net loss per common share is based upon the weighted average number of shares outstanding during the period, since inclusion of common equivalent shares would be anti-dilutive.

3. Cash equivalents consisting of certificates of deposit, treasury notes and money market funds are valued at cost which approximates market value.

   Marketable securities consisting of medium-term notes are also valued at cost which approximates market value.

4. On September 30,1991, the Company acquired the net assets of the Prenatal Diagnostic Laboratory of the Eunice Kennedy Shriver Center for Mental Retardation, Inc., located in Waltham, Massachusetts, for approximately $.9 million, including acquisition-related expenses, consisting of $.6 million in cash and a note payable of $.3 million which was paid on September 30, 1992. The acquisition has been accounted for as a purchase. The purchase price has been allocated to the net assets acquired (equipment and furniture) based on their estimated fair market value, which was approximately $90,000. The remainder of the purchase price was allocated to goodwill which is being amortized over twenty years.

FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Financial Condition and Liquidity

The company's cash and cash equivalents balance and marketable securities as of May 29, 1993 were $3,682,584. These funds, including the interest thereon, will be sufficient to meet the Company's short-term operational and capital needs.

During the thirteen (13) week period ended May 29, 1993, the company used approximately $823,000 primarily to support operational needs. For the thirty-nine (39) week period ended May 29, 1993, the company's funds decreased approximately $5,462,000. This reduction in funds primarily reflects the purchase of marketable securities of $2,068,000, including premiums, and approximately $2,800,000 cash loss from operations.

Results of Operations

For the thirteen week period ended May 29, 1993, operating revenue increased 24% when compared to the same period of last year and 34% when compared to the prior quarter of this year. Revenue from the research business increased approximately 31% when compared to the same period last year and 35% when compared to the prior quarter reflecting increased performance on several research contracts and grants. Revenue from the diagnostic testing business increased 50% when compared to the same period of last year and 27% when compared to the prior quarter reflecting primarily higher volume in the cancer testing segment of that business.

For the thirty-nine (39) week period ended May 29, 1993, operating revenue increased 25% when compared to the same period last year reflecting primarily higher volume in both the research and diagnostic testing segments of the business of approximately 26% and 47% respectively.

Royalty income for the thirteen (13) week period ended May 29, 1993 compared to the same period of last year decreased approximately 12% reflecting an inception-to-date adjustment of $55,000 last year resulting from the first royalty payment from Dow Chemical for sales by Pfizer, Dow's licensee, of recombinant chymosin. However, royalty income nearly doubled when compared to the prior quarter reflecting an increase in Pfizer's sales from last year and a year-to-date accrual adjustment to reflect the current sales level. Royalty income from Dow is accrued monthly but paid to us annually around May 1.

For the thirty-nine (39) week period ended May 29, 1993, royalty income increased 79% when compared to the same period last year again reflecting the same reasons stated above.

For the thirteen week period ended May 29, 1993, interest income decreased 69% when compared to the same period of last year and 33% when compared to the prior quarter reflecting a reduction in invested funds and lower interest rates. For the thirty-nine (39) week period ended May 29 , 1993, interest income decreased 51% when compared to the same period of last year again reflecting a reduction in invested funds.

Cost and Expenses

For the thirteen week period ended May 29, 1993, cost of revenue, as a percentage of operating revenue, increased 12% when compared to the same period last year reflecting primarily increased costs associated with building the diagnostic testing business, increased occupancy cost resulting from the relocation of our operations and increased overhead expenses. Cost of revenue, as a percentage of operating revenue, decreased 19% when compared to prior quarter reflecting primarily greater absorption of fixed overhead expenses. Cost of revenue, in absolute dollars, when compared to prior quarter and prior year increased 12% and 41% respectively reflecting higher sales volume and increased overhead expenses as outlined above.

For the thirty-nine (39) week period ended May 29, 1993, cost of revenue, both in absolute dollars and as a percentage of operating revenue, increased 41% and 12% respectively when compared to the same period last year reflecting higher sales volume, increased occupancy costs and overhead expenses.

For the thirteen (13) week period ended May 29, 1993, research and development expenses decreased approximately 73% both when compared to the same period last year and prior quarter reflecting the Company's decision to discontinue efforts in new test development within the diagnostic testing business in the third quarter of the current fiscal year.

For the thirty-nine (39) week period ended May 29, 1993, research and development expenses decreased approximately 16% when compared to the same period last year again reflecting discontinued efforts in new test development within the diagnostic testing business.

For the thirteen (13) week and thirty-nine (39) week periods ended May 29, 1993, selling, general, and administration expenses increased approximately 15% and 23% respectively when compared to the same periods last year, reflecting increased occupancy cost associated with the new facility, staffing of administrative support positions made vacant as a result of the sale of the biomedical products business on August 30, 1991, and increased cost associated with the recruitment and hiring of a new CEO for the Company.

Selling, general, and administration expenses increased approximately 10% for the thirteen (13) week period ended May 29, 1993 when compared to the prior quarter primarily reflecting the hiring of the new CEO, and increased business development expenses.

Part II

Item 1. Legal Proceedings

None

Item 2. Changes In Securities

None

Item 3. Defaults Upon Senior Securities

None

Item 4. Submission of Matters to a Vote of Security Holders

None

Item 5. Other Information

Subsequent to quarter-end, the Company announced that it has sold the net assets of its diagnostic testing business to Dianon Systems, Inc. The terms of the agreement were not disclosed.

Item 6. Exhibits and Reports on Form 8-K

a) Exhibits:

None.

b) Reports on Form 8-K

None.

DNA DRUG DISCOVERY

COLLABORATIVE RESEARCH, INC.

204 Second Avenue

Waltham, Massachusetts 02154

June 23, 1992

EXECUTIVE SUMMARY

Collaborative Research, Inc. (CRI) is the leading private, for-profit, human genome research establishment in the United States. CRI has been engaged in genome research from the very earliest days of the science. It is currently the recipient of thirteen separate grants and contracts which deal with various aspects of the Human Genome Project -- more than any other commercial institution -- and has been credited with a number of fundamental breakthroughs in the elucidation of genetic processes.

CRI believes that recent rapid progress in the technology of mapping and sequencing human genes and in using genetic information to elucidate diseases and potential therapies, has created very large commercial opportunities. CRI will be the first company to mount a broadly-gauged research program aimed at the early discovery of a wide range of gene-based therapies, diagnostic tools, and other commercial products based on Human Genome Project research.

It is CRI's intention to supplement its internal financial resources by raising new capital to fund a three-year program of research and commercial development. This paper is a concept paper to alert selected potential investors and financial intermediaries to the nature and scale of the opportunity.

In the sections that follow, we discuss in summary form:

- The background, accomplishments, and capabilities of CRI;
- Recent commercially-relevant progress in genome research;
- The scale of the commercial opportunity; and
- CRI's commercialization strategy.

COMPANY BACKGROUND, ACCOMPLISHMENTS, AND CAPABILITIES

CRI was founded in 1961 by Dr. Orrie M. Friedman, then the Helena Rubenstein Professor of Chemistry at Brandeis University. The purpose of the company was to conduct federally sponsored drug development research. CRI gradually expanded its activities into the production and marketing of biochemicals and cell culture for the research laboratory community. In 1982, it successfully completed an initial public offering to finance an expansion of its research in the rapidly advancing fields of molecular biology and molecular genetics.

Today, CRI is one of only five large-scale DNA sequencing laboratories in the United States and is the only commercial laboratory in the group. Although other for-profit companies are carrying out Human Genome Project work, CRI -- with over forty full-time scientists working on genome research -- is the only one with the essential critical mass of scientists and laboratory capabilities to engineer rapid, broad-scale advances in the field.

CRI's record of scientific accomplishment includes:

- CRI published the first detailed, genetic linkage map of the human genome (the so-called nine-centimorgan map) -- the product of many years of work involving the collective output of several laboratories, under the direction of CRI. CRI's work on genome mapping has been hailed as one of the major recent breakthroughs in genome science. They began work on the human genome linkage map in 1983, long before the idea of the Human Genome Project was considered seriously by most scientists.

- CRI introduced one of the first commercial genetic tests for prenatal diagnosis of cystic fibrosis. The test was based on a genome "marker" it discovered and had used in a collaboration to localize the gene responsible for cystic fibrosis to a region on chromosome 7;

- CRI was one of the very first companies to produce commercial recombinant DNA products. Its scientists cloned bovine growth hormone in both yeast and bacteria, the cheese-making enzyme rennin in yeast, and pro-urokinase in animal cells.

- CRI currently holds thirteen major Human Genome Project grants and contracts which are summarized in Appendix I.

CRI also is experienced in the manufacture of protein drugs under strict FDA and GMP guidelines and possesses state-of-the-art technology for the manufacture of recombinant-DNA-derived drugs in animal cell culture, yeast and bacteria.

Current genome-related staffing comprises: 15 Ph.Ds., 4 computer scientists in informatics, and 30 technicians. CRI's activities cover all technical aspects of the Human Genome Project. We believe this represents the largest commercial genome research establishment in the country. Over the medium-term future, CRI plans to increase the scale of its research staff by fifty percent.

PROGRESS IN GENOME RESEARCH:

A SUMMARY

Overview

The Human Genome Project is a $15 billion, fifteen-year effort, coordinated by the United States government, but involving research laboratories throughout the entire world. As is well known, the genetic information of all living organisms is written in DNA, the famous "double helix" first described by Watson and Crick in 1953. The sequence of nucleotides, or base pairs, making up the ladder of the double helix, symbolized by the letters A,T,G, and C, spell out the precise genetic instructions governing the growth, development, and daily functioning of all organisms -- that is, of all animals and plants, as well as of the bacteria and viruses that infect them.

The goal of the Genome Project is to determine the entire base pair sequence of human DNA and those of a number of other organisms of medical, agricultural, and scientific interest. It is a formidable undertaking. The human genome contains some 3 billion base pairs, equivalent to a library of 5,000 books. Complete success will require advances in a host of technologies, from computer software to store and cross-reference sequences to orders-of-magnitude improvements in existing mapping and sequencing technology.

Although the Genome Project was greeted with skepticism among certain sectors of the scientific community, recent progress is rapidly quelling doubts. The rapid pace of improvement in DNA deciphering technology suggests that commercial opportunities will proliferate. Later in this account we will provide a number of examples.

Disease-Focused Genome Research

Locating a specific gene takes place in two steps, mapping and sequencing. DNA mapping is a set of technologies to locate genes of interest on the genome -- to provide, in effect, a federal-highway level map of the terrain. CRI is a world leader in mapping technology and has assembled a substantial body of proprietary art and related capabilities in genome mapping.

Sequencing is the process of determining the exact order of DNA nucleotides, the DNA sequence. Once a gene has been approximately located on the genome through mapping, the painstaking task of sequencing sizable regions of the genome is necessary to locate the gene precisely and to determine the nucleotide sequence that makes up the gene.

The formidable difficulties presented by the Genome Project relate, in part, to the Project's insistence on decoding the entire human DNA sequence, regardless of its intrinsic interest for medical or other research. Much faster results of commercial interest can be obtained, however, by focusing on specific areas of the genome that are known to harbor genes of great intrinsic interest. CRI has therefore created a substantial research capability, working in parallel with its Genome Project research, to apply the burgeoning Genome Project mapping and sequencing technologies to genes of specific commercial interest. The projected fund-raising will be in order to enhance and expedite that effort. As the only commercial enterprise among the handful of leading world centers in Genome Project mapping and sequencing research, CRI therefore provides a unique opportunity for investors to participate at the very outset of an enormously promising venture.

THE COMMERCIAL POTENTIAL OF DNA RESEARCH

Understanding the genetic basis of disease opens the door to many powerful medical technologies, ranging from extremely precise diagnostic tools to test for the presence of, or predisposition to, a specific disease; DNA therapies to disable, or replace, a defective gene; new drug design; and procedures to predict toxicity reactions from conventional drug therapies. The Table below provides a brief overview of the scale of commercial opportunities from DNA research.

TABLE I

THE COMMERCIALIZATION OF DNA RESEARCH

Commercial Area	Applications
Medicine	
• DNA drug discovery for genetic diseases; diseases with a genetic component; and infectious diseases	• Correct genetic defects; cure active disease; alleviate symptoms; disease prevention.
• Gene therapy	• Replace defective genes to prevent genetic disease
• Vaccines for infectious diseases	• Prevent disease; alleviate symptoms
• Pharmacogenetics for drugs with genetically determined side-effects	• Rescue banned drugs; predict side-effects in individual patients
• Diagnostics	• Diagnose genetic disease: predict potential for and severity of disease; disease prevention
Agriculture	
• Animal and plant breeding	• Determine important genes for subsequent genetic engineering; guide classical breeding
• Veterinary medicine	• Many of the same uses as in human medicine
Manufacturing	
• DNA drugs	• (Uses described above)
• DNA probes for diagnostics	• (Uses described above)

The Table below presents a list of diseases and their incidence where CRI drug discovery research is already substantially advanced.

TABLE II

DISEASES IN PRESENT DNA DRUG DISCOVERY RESEARCH AT COLLABORATIVE RESEARCH

Short Term Research	Incidence
• Tuberculosis	• 1.7 billion victims worldwide
• Non-insulin dependent diabetes	• 12 million living victims in U.S.
• Meduallary thyroid carcinoma (MEN 2A)	• 15,000 living victims in U.S.
• Facioscapulohumeral muscular dystrophy (orphan drug status candidate)	• 12,500 living victims in U.S.
Long Term Research	
• Bipolar affective disorder	• 250,000 affected in U.S.
• Schizophrenia	• 2.5 million living victims in U.S.
• Male patterned baldness	• 20 million affected in U.S.
• Hypertension	• 58 million sufferers
• Insulin dependent diabetes	• 500,000 living victims in U.S.
• Asthma	• 10 million sufferers in U.S.
• Prostate Cancer	• 8 million cases in U.S.

There is a long list of other diseases amenable to DNA drug discovery, including virtually all viral and other microorganism-caused diseases. Neglecting these, a sampling of major diseases that are believed to have their origin in genetic defects are presented below.

TABLE III

POTENTIAL CANDIDATES FOR COLLABORATIVE'S DNA DRUG DISCOVERY RESEARCH

Major Diseases with Genetic Components	Incidence
• Cancers (all)	• 1 million new cases per year
• Heart disease (familial hypercholesterolemia)*	• 470,000 living victims
• Diabetes*	• 10 million living victims
Major Genetic Diseases	
• Huntington's disease	• 25,000 living victims
• Polycystic kidney disease	• 70,000 living victim
Mental Illness and "Well-Being" Conditions	
• Manic Depression	• 3.3 million living victims
• Alcoholism*	• 10 million living victims

*Long-term research candidates.

Recent progress in three specific disease classes bears further comment as an illustration of the power of genetically-grounded DNA research:

Cystic Fibrosis (CF). CF stems from a genetic defect which leads to a deficiency in a protein, CFTR, that regulates mucus secretion in the lungs. In victims, excessive secretions causes infection and lung damage, and early death. It is the most common genetic disease among caucasians. The gene was isolated and sequenced in 1989.

Recently, it was demonstrated that the introduction of normal CFTR genes into the cells from the lining of the lung partially reversed the course of the disease symptoms in cells grown in tissue culture. Researchers are currently concentrating on developing inhalant-delivered CFTR proteins or genes as well as various forms of gene therapy, in the hope of achieving full cure.

Myotonic Dsytrophy (DM). DM, a common genetic disease with an incidence of approximately 1 in 8000, is characterized by muscular spasms (myotonia) and progressive muscle weakness. The disease is known to become more severe in subsequent generations of the affected families (so-called genetic anticipation).

An intensive gene mapping and DNA sequencing effort identified a specific repeating triplet CTG,CTG,CTG,CTG... as the source of the genetic defect. Furthermore, in individuals with a greater number of CTG repeats, the more severe is the disease, and the number of repeats increases with subsequent generations. This discovery allows the development of diagnostic tests to predict disease severity.

Furthermore, a variety of other genetic diseases, such as fragile X syndrome and Kennedy disease, are now also known to be associated with repeated triplets. Similarly, these observations open potentially very fruitful research directions.

Non-Insulin-Dependent Diabetes Mellitus (NIDDM). NIDDM affects 5% of the world's population. One form of this disease, characterized by intolerance to sugar (glucose), occurs as maturity-onset diabetes of the young (MODY) and may account for up to 20% of NIDDM patients. MODY can be caused by several different genes, one of which has already been identified. The glucokinase gene has been shown to be responsible for MODY in a number of French families. Another gene responsible for MODY has been localized to the long arm of chromosome 20. Collaborative Research has identified genetic markers which flank this gene on chromosome 20 and define the region in which it is contained. As a result, CRI is in an ideal position to clone this disease gene.

Mycobacterium tuberculosis. Collaborative Research is one of five laboratories in the United States doing large scale DNA sequencing. As the only commercial laboratory in this group, it is currently working on determining the complete nucleotide sequence of the causative agent of tuberculosis. This disease, which had been thought to be completely under control, is now beginning to infect an ever-increasing number of people in the United States. Individuals with compromised immune systems are particularly susceptible to this disease. Strains resistant to the antibiotics currently used to treat the disease are now being reported with greater frequency. The work being done at Collaborative Research will permit the development of new vaccines as well as greatly help the development of new therapeutic agents for treating this disease.

There are a number of new reports in the literature for a number of diseases, including cancers and heart disease, where the Human Genome Project is yielding knowledge needed for drug design, i.e. disease mechanism; targets for drugs; drug candidates; new therapies; and diagnostic procedures. Selected literature references are provided in Appendix II.

THE CRI STRATEGY

CRI will take full advantage of its leadership position in Human Genome Project research to identify and exploit pharmaceutical development opportunities of outstanding commercial interest. In particular, it will focus on creating composition of matter and use intellectual property rights, which confer a strong strategic position.

Exploitation of intellectual property rights derived from genome-based research, depending on the circumstances, could take the form of:

- Direct development and manufacture of pharmaceuticals by CRI, making use of CRI's FDA GMP capabilities. This strategy would most likely be pursued in the case of orphan drugs, where commercial quantities are well within CRI's manufacturing capabilities.

- Research and development joint ventures, coupled with subsequent royalty participation or other financial interests.

- Licensing of rights to large pharmaceutical companies.

Proceeds of the envisioned fund raising would be directed to significantly increasing its present over 40-person research effort, with the intention of focusing on a small number of carefully chosen diseases, comprising a mix of short-term orphan drug designated diseases, and major diseases for longer-term development. Major investment categories would include:

- Facilities construction

- Operating expenses for three years

- Collaborative Diagnostics

APPENDIX I

SUMMARY OF MAJOR HUMAN GENOME PROJECT GRANTS AWARDED TO COLLABORATIVE RESEARCH

1. NATIONAL CENTER FOR HUMAN GENOME RESEARCH

- Develop "Framework" Maps for Human Chromosomes 10 and 20
- Construct a Physical Map for Human Chromosome 10
- Determine the Capability of Computer-Assisted Multiplex Sequencing
- Develop Polymorphic Alu Sequences as Genetic Markers
- Convert Southern Based Polymorphic Markers into PCR Based Polymorphisms

2. NATIONAL CANCER INSTITUTE

- Clone the Gene Responsible for Medullary Thyroid Carcinoma (MEN2A)

3. NATIONAL INSTITUTE OF MENTAL HEALTH

- Map the Gene(s) Responsible for Bipolar Affective Disorder

4. NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

- Sub-Clone DNA Fragments and Prepare DNA for Automated Sequencing

5. NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

- Map and Clone the Genes Responsible for Non-Insulin Dependent Diabetes

6. NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCE

- Convert VNTR Loci into PCR-Based Probes and Develop a Population Database for Them

7. MUSCULAR DYSTROPHY ASSOCIATION

- Clone the Gene Responsible for Facioscapulohumeral Muscular Dystrophy

8. WORLD HEALTH ORGANIZATION

- Determine the Feasibility of Sequencing the Genomes of Mycobacterium leprae and M. tuberculosis

9. DEPARTMENT OF ENERGY

- Construct Chimera-Free, High Copy Number YAC Libraries

APPENDIX II

LITERATURE REFERENCES FOR RECENT REPORTS RELATING TO HUMAN GENOME PROJECT DRUG DISCOVERY

Cystic Fibrosis.

Rommens, J.H., M.C. Ianuzzi, B.-S. Kerrem, M.L. Drumm, M. Dean, R. Rozmehel, J.L. Cole, D. Kennedy, N. Hidaka, M. Zsiga, M. Buchwald, J.R. Roirdan, L.-C. Tsiu and F.C. Collins (1989). Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping. Science, 245, P.1059-1065.

Gregory, R.J., S.H. Cheng, D.P. Rich, J. Marshall, S. Paul, K. Hehir, L. Ostedgaard, K.W. Klinger, M.J. Welsh, and A.E. Smith (1990). Expression and Characterization of the Cystic Fibrosis Transmembrane Conductance Regulator. Nature, 347, p.382-386.

Rich, D.P., M.P. Anderson, R.J. Gregory, S.H. Cheng, S. Paul, D.M. Jefferson, J.D. McCann, K.W. Klinger, A.E. Smith and M.J. Welsh (1990). Expression of the Cystic Fibrosis Transmembrane Conductance Regulator Corrects Defective Chloride Channel Regulation in Cystic Fibrosis Airway Epithelial Cells, Nature, 347, p.358-363.

Cheng, S.H., R.J. Gregory, J. Marshall, S. Paul, D.W. Souza, G.A. White, C.R. O'Riordan and A.E. Smith (1990). Defective Intracellular Transport and Processing of CFTR is the Molecular Basis of Most Cystic Fibrosis. Cell, 63, p.827-834.

Dalemans, W., P. Barbry, G. Champigny, S. Jallat, K. Dott, D. Dreyer, R.G. Crystal, A. Pavirani, J.-P. Lecocq, and M. Lazdunski (1991). Altered Chloride Channel Kinetics Associated with the Delta-F508 Cystic Fibrosis Mutation. Nature, 354, p. 526.

Myotonic Muscular Dystrophy.

Mahadevan M., C. Tsilfidis, L. Sabourin, G. Shutler, C. Amemyia, G. Jansen, C. Neville, M. Narang, J. Barcelo, K. O'Hoy, S. Leblond, J. Earle-Macdonald, P.J. de Jong, B. Wieringa (1992). Mytonic Dsytrophy Mutation: An Unstable Repeat in the 3' Untranslated Region of the Gene. Science, 255, p.1253- 1255.

Fu, Y.-H., A. Pizzuti, R.G. Fenwick Jr., J. King, S. Rajnarayan, P.W. Dunne, J. Dubel, G.A. Nasser, T. Ashizawa, P. de Jong, B. Wieringa, R. Korneluk, M.B. Perryman, H.F. Epstein and C.T. Caskey (1992). An Unstable Triplet Repeat in a Gene Related to Myotonic Muscular Dystrophy. Science, 255, p.1256-1258.

Collaborative Research Incorporated

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ORRIE M. FRIEDMAN, PH.D.
Chairman of the Board

A Boston

October 15, 1993

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

Dear Alfred:

It was wonderful seeing you again last night. The meeting suddenly turned the clock back forty-five years to the basement at Converse at Harvard a long time ago.

As promised I'm sending the enclosed packet of information on Collaborative Research, Inc. which I believe will give you a sense of what the Company is as we begin refashioning it into a dynamic instrument for the discovery of new pharmaceuticals in the new era in which we are now entering. We have the money to survive but we do not have the financial resources that are needed to enable us to develop the new drugs on our own rather than to seek partnerships with the pharmaceutical industry.

In any event, if you are interested I think you would be well served by a visit where you could see what we do first hand.

In any event, when next you come to Boston with your dear wife let me know as Laurel and I would be delighted to get together with you.

Best regards.

Sincerely,

Orrie M. Friedman

ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

October 22, 1993

Dr. Orrie M. Friedman
Chairman
Collaborative Research Inc.
100 Beaver Street
Waltham, Massachusetts 02154

Dear Orrie:

It was so good to see you last week. Now I have to thank you for that most interesting package on Collaborative Research. As I am just leaving on two long trips from which I will not return until December 26th, I will study the package upon my return.

I visit the Boston area once or twice each year, and the next time I hope to have a chance to visit with you at Collaborative Research.

Best wishes.

Sincerely,

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

October 22, 1993

Dr. Liane Reif-Lehrer
6 Mason Street
Lexington, Massachusetts 02173

Dear Dr. Reif-Lehrer:

Thank you for your letter of October 9th.

Your son's oil paintings look most interesting and are very reasonably priced.

the next time I visit the Boston area, I will plan to visit with you and him as I much prefer buying paintings on seeing the originals.

I return the slides as you requested.

All good wishes.

Sincerely,

Enclosures

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

Liane Reif-Lehrer, PhD

6 Mason Street, Lexington, MA 02173
Tel: 617-861-0989, 863-1117; Fax: 617-674-0436

October 9, 1993

Dr. Alfred Bader
Alfred Bader Fine Arts
Astor Hotel Suite 622
924 East Juneau Avenue
Milwaukee, Wisconsin 53202

Tel: 414-277-0730; Fax: 414-277-0709

Dear Dr. Bader:

Thank you for your letter of October 1 and your interest in my son Damon's work.

In response to your question about the price of the self portrait (of which you saw a photocopy), I am sending you slides of that painting and 9 other paintings by Damon, together with a list of the sizes and prices of the paintings.

Perhaps it would interest you to know that Damon illustrated and hand made a limited edition book in 1992. The book, *Aphorisms*, has nine unbound woodcut prints by Damon which illustrate eight aphorisms by Wm. Cole. The book has been purchased by the Houghton Library at Harvard University, the Boston Public Library, the New York Public Library and the Dartmouth College Library. The Fogg Art Museum purchased an artist's proof of one of the woodcut prints. The price for the standard edition (single suite of prints) of the book is $500. I am enclosing a prospectus for the book and photocopies of two of the prints.

For your convenience, I am enclosing a self-addressed stamped envelope for return of the slides.

Sincerely,

Liane Reif-Lehrer

Liane Reif-Lehrer

APHORISMS

by William Cole

Woodcuts by Damon Lehrer

This book was set in Garamond types
at The Bow & Arrow Press,
Cambridge, Massachusetts.

Eighty-nine copies of this book were printed on Arches Cover Buff paper.

Two copies, for the author and the artist, with a suite of the woodcuts in sanguine, a suite in black on Japanese kozo paper, a suite of impressions of the canceled blocks, and various preparatory drawings and proofs;

Ten copies, numbered I-X, with a suite in sanguine and a suite in black on kozo;

Twenty-five copies, numbered XI-XXXV, with a suite in sanguine;

Fifty copies, numbered 1-50;

Two copies, numbered H.C. I and H.C. II, with a suite in sanguine, for The Bow & Arrow Press.

Printed by hand in June, 1992.

Paintings by Damon Lehrer

6 Mason Street
Lexington, MA 02173
617-861-0989
Fax: 674-0436

#	Description	Medium	Approx. Size	Price*
1	Self-portrait	Oil on masonite	11" x 16"	$700
2	Man with turban, cat & marble	Oil on masonite	9" x 12"	$350
3	Young man with brush cut	Oil on canvas	16" x 20"	$700
4	Woman in red	Oil on canvas	18" x 22"	$700
5	Self-portrait in orange robe	Oil on canvas	18" x 22"	$800
6	Watching TV	Oil on canvas	52" x 52"	$2,500
7	A study for Watching TV	Oil on canvas	30" x 30"	$400
8	The Stabbing	Oil on canvas	48" x 52"	$2,500
9	Woman calling out the window	Oil on canvas	18" x 22"	$700
10	Woman with turban	Oil on masonite	9" x 12"	$350

*Prices do not include cost of packaging/shipping/insurance

Tech-Write Consultants/Erimon Associates
Box 645, Belmont, MA 02178; (617) 863-1117
Liane Reif-Lehrer, Ph.D., President

March 4, 1994

Dr. Stephen Branca, PhD
Director, Publications & New Products
Aldrich Chemical Company, Inc.
PO Box 355
Milwaukee, Wisconsin 53201

Dear Dr. Branca:

I have been very involved with writing my new book for many months and was not able to take time to get some more slides of Damon's art work to you as we had discussed some months ago. But I have now picked out 30 slides to send.

Perhaps Dr. Bader would also be interested in seeing these slides. I would appreciate it if you would pass the slides on to him at your convenience and ask him to please return them in the envelope provided.

Please let me know whether any of the enclosed slides are of interest to you. We look forward to seeing the July issue when it comes out.

Should you want to contact me, please be aware that I will be away March 5 to 11 and April 15 to 30.

Sincerely,

Liane Reif-Lehrer

Liane Reif-Lehrer
FAX # 617-674-0436 (press the * button to get a fax tone)

Alfred:

I'm finished looking at them and have passed them on to you. Selected one for a future Acta. Best Regards!

Steve
3/21/94

ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

March 22, 1994

Dr. Liane Reif-Lehrer
6 Mason Street
Lexington, Massachusetts 02173

Dear Dr. Reif-Lehrer:

Dr. Steven Branca stopped by my gallery this morning and left me the 30 slides of works by Damon Lehrer which you sent to him. To me, they look like very attractive works, particularly the single figure portraits, and I was happy to see that Dr. Branca has selected one for a future Aldrichimica Acta.

I handle mainly old master paintings in my gallery, and hence am attracted to Damon Lehrer's works. I visit the Boston area about once a year, and it would give me great pleasure if I could see some of the original works.

All good wishes.

Sincerely,

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