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Record Group/Collection: George H.W. Bush Presidential Records
Collection/Office of Origin: Science and Technology Policy, Office of (OSTP)
Series: Bromley, D. Allan, Files
Subseries: General Science Files

OA/ID Number: 62038
Folder ID Number: 62038-003

Folder Title:
Life Sciences: General [3 of 4] [1991]

Stack:

Row:

Section:

Shelf:

Position:

0

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"CORRESPONDENCE TRACKING"

TYPE: ACTION

DOCUMENT NUMBER: 9121255

FROM: SORIAN, Richard: HEALTHCARE INFORMATION CENTER

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 04/15/91

SUBJECT: REQUEST TO REVIEW A COPY OF YOUR ENTRY IN THE 1991
EDITION OF FAULKNER & GRAY'S "THE HEALTH CARE 500"

ASSIGNED TO: D. Allan Bromley

*mq Pls. ask DAH if this
is legit. Note the request
for our annual budget ??
Is this a pub that DAB needs
to be associated w? Pls.
advise.*

ACTION REQUIRED: AS APPROPRIATE

SENDER'S DUE DATE:

OSTP DUE DATE:

05/11/91

DATE COMPLETED:

See note from

COPIES TO:

*DA Henderson
close out*

*T.U.
Jamar
4/30*

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 04/26/91

FILE: ~~MISCELLANEOUS~~
P- Life Sciences

Alamas -

This is just one of a whole host of publications designed to generate revenue for the publishers. It is not a reference guide which I would recommend or would access. There is no harm in appearing in it. I wouldn't bother to reply.

DA

9121255

RECEIVED

91 APR 26 P 1: 09

OFFICE OF THE
DIRECTOR

F&G

Healthcare Information Center

Faulkner & Gray, Inc.
1133 Fifteenth Street, NW
Suite 450
Washington, DC 20005
202/828-4148

April 15, 1991

Dear Dr. Bromley:

In 1990, you were included in the premier edition of Faulkner & Gray's "The Health Care 500," a guide to the most influential health policy makers in the United States. Let me again offer my congratulations and my appreciation for your assistance in putting together a very successful directory that has already become a standard in offices across the country.

As I begin preparation of the 1992 edition, I am again requesting your assistance. I have enclosed a copy of your entry in the 1991 edition. Please check for any inaccuracies or omissions. If there are any changes necessary, please send them to me along with a current C.V. as soon as possible.

To make each entry as useful to our readers as possible, we need up-to-date information regarding the size of your operation, its annual budget, its areas of emphasis, and its future directions. If that kind of information is not included in your C.V., would you please provide it? To avoid follow-up telephone calls, please check to make sure the material you send includes:

- name and title
- current business address, telephone number, and fax number
- the universities you attended, the degrees you obtained, and the years in which you obtained them
- year of birth
- a black and white photograph

Could you also suggest two or three individuals in your sector of the health care field who you believe should be included in the next edition? As an expert in your field you are most likely to know the leaders and the up-and-comers. If you have them, please include an address and/or telephone number to assist my office in contacting them.

I thank you ahead of time for your assistance and look forward to hearing from you in the near future.

Sincerely,



Richard Sorian
Executive Editor

Enclosure

D. Allan Bromley
Director
Office of Science & Technology Policy
The White House
Washington DC 20006
Phone: 202/456-7116
Fax:

Degrees: B.S. (1948), M.S. (1950) Queens University; Ph.D.
University of Rochester (1952)
Born: 1926

An internationally acclaimed nuclear physicist, Bromley is on leave from Yale University to serve as President Bush's chief adviser on science and technology issues. During his lengthy career, he has carried out pioneering studies on the structure and dynamics of nuclei and is considered the "father" of modern heavy ion science. An outstanding teacher, Bromley has published more than 450 papers in science and technology and edited 18 books. Under President Reagan, Bromley led several international missions to achieve bilateral cooperation in science and technology.

"CORRESPONDENCE TRACKING"

TYPE: ACTION

DOCUMENT NUMBER: 9121026

FROM: JOHNSON, R. Jerry:POLYSTYRENE PACKAGING COUNCIL, INC.

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 04/05/91

SUBJECT: REQUEST TO INVESTIGATE THE EPA'S DECISION TO PLACE
STYRENE IN GROUP C OF EPA'S CLASSIFICATION SYSTEM.

ASSIGNED TO: Dr. Henderson

ACTION REQUIRED: AS NECESSARY

SENDER'S DUE DATE: OSTP DUE DATE: 04/22/91

DATE COMPLETED: -----

COPIES TO: D. Allan Bromley

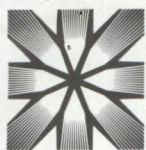
WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 04/08/91

FILE: P-LIFE SCIENCES



POLYSTYRENE PACKAGING COUNCIL, INC.

1025 CONNECTICUT AVE., NW SUITE 508 WASHINGTON, DC 20036 TEL: 202/822-6424 FAX: 202/331-0538

9/2/026

RECEIVED

91 APR 8 9:39

OFFICE OF THE
DIRECTOR

April 5, 1991

The Honorable D. Allan Bromley
Assistant to the President
for Science and Technology
17th and Pennsylvania Avenue, NW
Suite 358
Washington, DC 20506

Dear Mr. Bromley:

We are writing to ask you to investigate the Environmental Protection Agency's apparent decision to place styrene in Group C of EPA's classification system, labeling it a "possible carcinogen."

The Polystyrene Packaging Council, which represents manufacturers, fabricators and users of polystyrene food service and protective packaging, finds this decision misguided and scientifically unfounded.

Styrene has been studied exhaustively, and the preponderance of scientific evidence demonstrates that styrene causes no disease of any kind. Long-term epidemiological studies of 50,000 workers show no increase in cancer or any other disease among those exposed daily to occupational exposure levels of styrene.

The EPA itself has acknowledged the unscientific basis for its decision with its admission that scientific studies do not support setting any potency assessment.

Styrene is an organic substance that occurs naturally in foods from fruit to nuts, including apples, strawberries, grapes, tomatoes, milk, eggs, olives, nuts and honey. Styrene monomer conversion into polystyrene is such a complete polymerization process that exposure to styrene from polystyrene product use is in the very low parts per billion range. This is about the same as exposure from eating a fresh strawberry, and much lower than naturally occurring levels in many other foods and beverages.

The EPA decision to classify styrene contradicts the sound judgment of every other government agency that has analyzed the substance. EPA's own Office of Drinking Water concluded only three months ago that the evidence did not support classification of styrene as a carcinogen.

Letter to D. Allan Bromley
April 5, 1991
Page Two

Similarly, the Occupational Safety and Health Administration and the National Institute of Occupational Safety and Health also have decided that there is insufficient evidence to classify styrene as a carcinogen. In addition, the twelve nation European Community has determined that styrene should not be labeled, classified or regulated as a carcinogen.

A possible carcinogen classification could generate public alarm about exposure to styrene from many of the healthful foods in their diet. In fact, given EPA's admission that scientific evidence does not support setting a maximum dosage level, it would be impossible for consumers to make intelligent use of this decision.

Unfortunately, the polystyrene industry has now been caught in the quagmire of the EPA's irrational and illogical classification system. A possible carcinogen classification could have a devastating effect on the \$2 billion polystyrene industry, including 100,000 workers. Polystyrene, in durable and packaging forms, accounts for about 65 percent of styrene usage worldwide.

Industry produces five billion pounds of polystyrene annually in regulated and safe working conditions. We are confident that the use of styrene to manufacture polystyrene poses no cancer-related risk to our employees or to consumers of polystyrene products. In fact, polystyrene contributes to the public health because of its unparalleled sanitary and insulating qualities.

The manufacture of polystyrene is a highly efficient process and a unique conserver of materials. Data for air, water and solid waste emissions show there is extremely small waste or unused material in the manufacture of both resin and finished products. Polystyrene also is the only food service packaging being commercially recycled, and is a food packaging material that can be recycled back into food packaging, helping to close the recycling loop.

More than \$10 million has been committed to support research on the health effects of styrene. The decision to classify styrene in advance of adequate data from ongoing studies is unwarranted and unnecessary.

It would be a miscarriage of justice for this industry or any other to be damaged by an EPA decision that lacks grounding in science and fails every test of sensible public policy. We urge you to contact Administrator Reilly to question EPA's action and to encourage EPA not to classify styrene at this time.

Letter to D. Allan Bromley
April 5, 1991
Page Three

Thank you for your attention.

Sincerely,

POLYSTYRENE PACKAGING COUNCIL, INC.

A handwritten signature in cursive script, appearing to read "R. Jerry Johnson".

R. Jerry Johnson
Executive Director

RJJ/sf
LTR114s

Mary

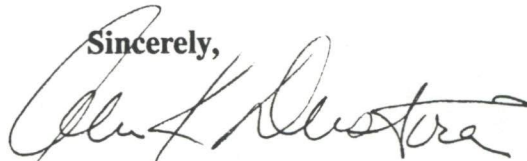
EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

June 24, 1991

Dear Mr. Johnson:

Thank you for your letter dated April 5, 1991 to Dr. Bromley concerning the Environmental Protection Agency (EPA) proposal to classify styrene as a Group C possible carcinogen. It is our understanding that this proposal is still undergoing a risk assessment analysis by EPA. Our staff will continue to monitor this issue and stay informed of EPA's work regarding this proposal.

Sincerely,



Alicia K. Dustira, Ph.D.
Senior Policy Analyst

cc: Ms. Sutton

R. Jerry Johnson
Executive Director
Polystyrene Packaging Council, Inc.
1025 Connecticut Avenue, N.W.
Suite 508
Washington, D.C. 20036

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION

DOCUMENT NUMBER: 9120979

FROM: ZAMARIA, Rose: THE WHITE HOUSE

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 04/02/91

SUBJECT: MESS PRIVILEGES AND A WHITE HOUSE PASS HAVE BEEN
APPROVED FOR D.A. HENDERSON.

ASSIGNED TO:

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO: D. Allan Bromley
Dr. Henderson

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 04/03/91

FILE: *P* LIFE SCIENCES

THE WHITE HOUSE
WASHINGTON

Date: 4/2/91

TO: D. ALLAN BROMLEY

FROM: ROSE ZAMARIA *Rz*
Deputy Assistant to the President and
Director of White House Operations

I am pleased to advise that Mess privileges and a White House pass have been approved for D.A. Henderson. He should receive the guidelines on using the Mess within the next few days. Secret Service will notify Dr. Henderson when his White House pass becomes available.

OFFICE OF THE
DIRECTOR

91 APR 3 P 3:56

RECEIVED

THE WHITE HOUSE
WASHINGTON

Date: 4/2/91

TO: D. ALLAN BROMLEY

FROM: ROSE ZAMARIA *Rz*
Deputy Assistant to the President and
Director of White House Operations

I am pleased to advise that Mess privileges and a White House pass have been approved for D.A. Henderson. He should receive the guidelines on using the Mess within the next few days. Secret Service will notify Dr. Henderson when his White House pass becomes available.

*Mary - cct to DAH +
files ←
DAB has a copy*

9120979

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION

DOCUMENT NUMBER: 9120983

FROM: WELDON, Virginia V.: MONSANTO

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 04/01/91

SUBJECT: INFORMATION ON THE SAFETY AND EFFICACY OF BST.

ASSIGNED TO:

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO: D. Allan Bromley
Life Sciences

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 04/03/91

FILE:  LIFE SCIENCES

9120983

Monsanto

VIRGINIA V. WELDON, M.D.
Vice President
Public Policy

Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167
Phone: (314) 694-3901

RECEIVED
91 APR 3 P 1:12
OFFICE OF THE
DIRECTOR

April 1, 1991

Dr. D. Allan Bromley
Assistant to the President
for Science and Technology and
Director, OSTP
Old Executive Office Building, Room 358
17th Street & Pennsylvania Avenue, NW
Washington, DC 20506

Dear Allan:

One more piece of good news on the safety and efficacy of BST. Recently the Committee for Veterinary Medicinal Products (CVMP) of the Commission of the European Communities concluded that the human safety, efficacy and usefulness of BST have been demonstrated. The findings of the CVMP are largely consistent with the National Institutes of Health Study of 1990, but go beyond that study in the area of animal safety.

As we have discussed, BST is the model by which the future products in the agricultural sector of biotechnology will be judged. A precedent has now been established in the scientific arena that science is the basis by which to judge products. We now await the decision in the political arena in Europe.

I look forward to seeing you in the future.

Sincerely,

Virginia



COMMISSION
OF THE EUROPEAN
COMMUNITIES

Brussels, 25 March 1991

Directorate-General
for Internal Market and Industrial Affairs

PRESS RELEASE

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

The 26th meeting of the Committee for Veterinary Medicinal Products was held in Brussels on 19-20 March 1991.

The Committee adopted its opinion on the application for authorization for SOMATECH, the MONSANTO recombinant BST product, intended to increase milk yields in dairy cattle. (1)

The Committee has unanimously agreed that SOMATECH is effective in producing an increase in milk yields in healthy animals in the range of 2.7-5.7 kg per day, is of the required quality and that residues of the product do not present any risk to the health of the consumer of milk or edible tissues from treated animals.

However, the Committee was unable to reach consensus on the acceptability of the product from the point of view of the safety of treated animals. Although the majority considered the manufacturer had provided sufficient guarantees on this point, several members considered that additional data was required on the incidence of mastitis and the importance of reactions at the injection site and the hygiene of this site before any definitive conclusion could be reached.

The Committee recommended that, in the event of authorization, the product should be made available only under veterinary supervision. It also recommended that authorization be subject to conditions to conduct further studies of the incidence of mastitis under practical conditions of use and to conduct a structured study of other adverse reactions to the product.

(1) Note for editors

The Monsanto application for SOMATECH was referred to the CVMP in accordance with Council Directive 87/22/EEC. This Directive provides for the systematic concertation of the examination of applications for authorization for veterinary medicines derived from biotechnology through the CVMP.

At the present time, opinions of the CVMP are not binding. However, Member States must obtain an opinion from the Committee and consider it before taking any decision to authorize or reject a veterinary medicine which is derived from biotechnology.

It should be noted that in accordance with Council Decision 91/61/EEC, Member States may not authorize the placing on the market of BST until 31 December 1991.

The Committee deferred detailed discussion of the application from the Lilly company in respect of SOMIDIBOVE, its BST product, because the company was in the process of transmitting additional information to the Member States.

The Committee adopted a unanimously favourable opinion on an application from the Upjohn company, submitted in accordance with Directive 81/851/EEC for ANTIROBE, clindamycin 25 mg, 75 mg and 150 mg capsules for dogs.

The Committee adopted the "Note for Guidance concerning the application of Chapter I of Part Two of Directive 81/852/EEC with a view to the demonstration of the safety of a veterinary medicinal product" (III/3897/90, final)

The Committee took note that the Commission had previously circulated for comments a draft Commission Directive laying down the principles and guidelines of good manufacturing practices for veterinary medicinal products (III/9066/90), together with draft supplementary guidelines for the manufacture of veterinary medicinal products other than immunological veterinary medicinal products (III/9097/90) and draft supplementary guidelines for the manufacture of immunological veterinary medicinal products (III/9258/90).

In addition the Committee noted that the Commission would shortly be circulating for comments;

- a draft Commission Directive to adapt the Annex of Directive 81/852/EEC to technical progress, and to extend the scope of the annex to cover immunological veterinary medicinal products;

"CORRESPONDENCE TRACKING"

TYPE: ACTION

DOCUMENT NUMBER: 9120956

FROM: KOLEHMAINEN, Jan: AMERICAN ACADEMY OF NEUROLOGY

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 03/26/91

SUBJECT: COMPLIMENTARY TICKETS FOR THE DECADE OF THE BRAIN
DINNER ON 04/24/91.

ASSIGNED TO: D. Allan Bromley

ACTION REQUIRED: PLEASE PHONE IN
REQUEST.

SENDER'S DUE DATE: 04/04/91

OSTP DUE DATE: 04/04/91

DATE COMPLETED: -----

COPIES TO: Life Sciences
Maryanne Bach

WHITE HOUSE TRACKING #:

CONTACT PERSON: CAROL CARLSON

REMARKS:

4/5/91 - asked Carol Carlson for 2 complimentary tickets!

DATE RECEIVED: 04/01/91

FILE: P-LIFE SCIENCES

4/8 Told AB

THE WHITE HOUSE

WASHINGTON

January 18, 1991

Dear Dr. Rowland:

Thank you for your letter of November 5 inviting me to be the evening speaker April 24 at the AAN annual meeting in Boston. I apologize for the much belated response.

I am happy to accept your invitation. As the time of the event approaches, my staff will contact your office to work out details with respect to my joining you and your colleagues for this very special event.

I very much look forward to the occasion.

Sincerely yours,

A handwritten signature in dark ink, appearing to read "D. Allan Bromley". The signature is fluid and cursive, with the first name "D. Allan" and the last name "Bromley" clearly distinguishable.

D. Allan Bromley
Assistant to the President
for
Science and Technology

Dr. Lewis P. Rowland
President
The Neurological Institute
710 West 168th Street
New York, New York 10032



AMERICAN ACADEMY OF NEUROLOGY™

RECEIVED

9120956
91 APR 1 P2:48

OFFICERS:

President
LEWIS P. ROWLAND, M.D.
New York, New York

President-Elect
ROGER N. ROSENBERG, M.D.
Dallas, Texas

Vice-President
ROBERT G. FELDMAN, M.D.
Boston, Massachusetts

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STEVEN P. RINGEL, M.D.
Denver, Colorado

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HAMILTON MOSES, III, M.D.
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Past-President
THEODORE L. MUNSAT, M.D.
Boston, Massachusetts

Editor of Journal
ROBERT B. DAROFF, M.D.
Cleveland, Ohio

Executive Director
JAN W. KOLEHMAINEN
Minneapolis, Minnesota

March 26, 1991

The Honorable Allan Bromley, Ph.D.
Assistant to the President for
Science and Technology Policy
Old Executive Office Building
17th Street and Penn Avenue, NW
Room 358
Washington, DC 20506

Dear Dr. Bromley:

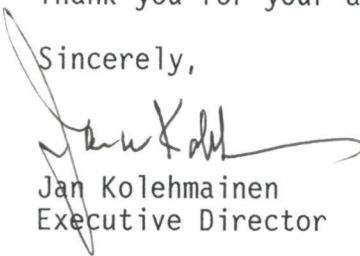
I am writing to let you know that the Academy will be pleased to provide complimentary tickets for the Decade of the Brain Dinner on Wednesday, April 24, for you and your guest.

If you need additional tickets for staff that will be accompanying you please let us know and we will accommodate your request. One additional ticket has been reserved for Alicia Dustira, Ph.D., in your office. We would appreciate receiving your ticket request by April 4. If you want to phone in your request, please contact Carol Carlson at the AAN office.

We will mail your ticket(s) to you as soon as we receive your confirmation call.

Thank you for your assistance with this.

Sincerely,


Jan Kolehmainen
Executive Director

JK/RH/ajd

cc: Harry Bradley
Dwight Smith
Carol Carlson



"CORRESPONDENCE TRACKING"

TYPE: INFORMATION

DOCUMENT NUMBER: 9120827

FROM: MASON, James O.: DEPARTMENT OF HEALTH & HUMAN SERVICES

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 03/18/91

SUBJECT: A PROPOSED WASHINGTON CONFERENCE ON BIOMEDICAL
APPROACHES TO ILLICIT DRUG DEMAND REDUCTION TO
ASCERTAIN ONGOING INTERNATIONAL RESEARCH ACTIVITIES.

ASSIGNED TO:

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO: Maryanne Bach
Life Sciences
D. Allan Bromley
Thomas Ratchford

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 03/21/91

FILE: *f* FCCSET*LIFE SCIENCES

DRUG ABUS E





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

MAR 18 1991

912 08 27
RECEIVED
Office of the Assistant Secretary
for Health
Washington DC 20201
MAR 29 10:19

The Honorable D. Allan Bromley
Chairman, Federal Coordinating Council
for Science, Engineering, and Technology
Office of Science and Technology Policy
Executive Office of the President
Washington, D.C. 20506

OFFICE OF THE
DIRECTOR

Dear Allan:

As the Chairman of the Federal Coordinating Council on Science, Engineering and Technology (FCCSET) Committee of Life Sciences and Health (LSH), I would like to present to you a synopsis of the most recent activities of a task force under our Brain and Behavioral Sciences Subcommittee. Enclosed is a copy of a cable that has been sent to query international interest in a proposed Washington conference on biomedical approaches to illicit drug demand reduction. The purpose of this conference is to bring together senior foreign government officials and scientists to exchange information on biomedical research approaches to the understanding and treatment of drug dependence and abuse. To date, the U.S. conducts the majority of the world's directed research in this area. In addition, the conference will provide an opportunity to ascertain ongoing international research activities and encourage future international scientific collaboration. Furthermore, this conference would serve to advance the goals of the President's National Drug Control Policy by strengthening a biomedical approach to drug demand reduction.

The National Institute on Drug Abuse has agreed to host this conference. If the cable reveals international interest, the 2-3 day conference would be held in Washington in the third quarter of this year and attendees would be expected to pay their own way.

The cable was developed and cleared by the Department of State, the Department of Health and Human Services, and the Office of National Drug Control Policy. In addition, we have discussed this conference with your staff.

Sincerely yours,

James O. Mason, M.D., Dr.P.H.
Assistant Secretary for Health
Chairman, Committee for Life
Sciences and Health

Enclosure

UNCLASSIFIED
Department of State

OUTGOING
TELEGRAM

PAGE 01 OF 02 STATE 066808 012258Z
ORIGIN QES-09

SHB9409

STATE 066808 012258Z
REQUESTED MLT MARCH 22, 1991. END SUMMARY.

SHB9409

INFO LOG-00 ADS-00 AMAD-01 ARA-00 DEAE-00 EAP-00 EUR-00
HNS-06 INM-00 INRE-00 INR-01 IO-19 NEA-00 NSCE-00
OIC-02 OIG-00 SS-00 /045R

9722

DRAFTED BY: QES/SCT: MQUEAR/TLONGC

APPROVED BY: QES/SCT: MPROCHNIK

INM: WJOLSON

OSTP: RLEVINSON

HNS: ECOOPER

EAP: MMEYERS

EUR: BMCKINLEY

ARA: MKOZAK

NEA: SKISH

ONDCP: AHOUGHTON

QES/S: JBORIGHT (NFC)

QES: RSMITH (INFO)

-----4800EE 012300Z /36

R 012256Z MAR 91

FM SECSTATE WASHDC

TO AMEMBASSY BEIJING

AMEMBASSY BELGRADE

AMEMBASSY BERN

AMEMBASSY BOMN

AMEMBASSY BRASILIA

AMEMBASSY BUENOS AIRES

AMEMBASSY CANBERRA

AMEMBASSY COPENHAGEN

AMEMBASSY HELSINKI

AMEMBASSY LONDON

AMEMBASSY MADRID

AMEMBASSY MEXICO

AMEMBASSY MOSCOW

AMEMBASSY NEW DELHI

AMEMBASSY OSLO

AMEMBASSY OTTAWA

AMEMBASSY PARIS

AMEMBASSY PRAGUE

AMEMBASSY ROME

AMEMBASSY STOCKHOLM

AMEMBASSY TEL AVIV

AMEMBASSY THE HAGUE

AMEMBASSY TOKYO

AMEMBASSY VIENNA

AMEMBASSY WARSAW

AMEMBASSY WELLINGTON

INFO RUEHBS/AMEMBASSY BRUSSELS

USMISSION USUN NEW YORK 0000

UNCLAS STATE 066808

E.C. 12356: N/A

TAGS: TPKY SNAR

SUBJECT: INVITATION RECOMMENDATIONS FOR AN INTENDED WASHINGTON
SCIENTIFIC CONFERENCE ON BIOMEDICAL APPROACHES TO ILLICIT DRUG
DEMAND REDUCTION

1. SUMMARY: THE DEPARTMENT REQUESTS ADDRESSEES TO
ASCERTAIN HOST GOVERNMENT INTEREST IN AND IDENTIFY

POSSIBLE INVITEES TO A PROPOSED 2-3 DAY MULTILATERAL
CONFERENCE IN WASHINGTON IN THE THIRD QUARTER OF THIS
YEAR ON INTERNATIONAL COLLABORATION IN BIOMEDICAL RESEARCH
ASPECTS OF ILLICIT-DRUG DEMAND REDUCTION. THE GOAL OF
THIS PROPOSED CONFERENCE IS TO ENCOURAGE COORDINATED
INTERNATIONAL COOPERATION IN THE SUBJECT AREA. POSTS
SHOULD DRAW ON THIS CABLE FOR BACKGROUND. REPLIES

2. THE DEPARTMENT (DES, IN CONJUNCTION WITH INMI HAS
RECOMMENDED AND THE NATIONAL INSTITUTE FOR DRUG ABUSE
(NIDA), WITH THE SUPPORT OF THE WHITE HOUSE OFFICE OF
NATIONAL DRUG CONTROL POLICY (ONDCP), HAS UNDERTAKEN TO
HOST A PROPOSED 2-3 DAY INTERNATIONAL CONFERENCE IN THE
THIRD QUARTER OF THIS YEAR IN WASHINGTON ON INTERNATIONAL
COLLABORATION ON BIOMEDICAL RESEARCH APPROACHES TO
ILLICIT-DRUG DEMAND REDUCTION. THE INTENT IS TO BRING
TOGETHER A NUMBER OF SENIOR FOREIGN GOVERNMENT SCIENCE
POLICY OFFICIALS TO INTERACT, TO EXCHANGE INFORMATION ON
BIOMEDICAL/SCIENTIFIC APPROACHES TO THE NATURE OF
ADDICTION AND ILLICIT-DRUG DEMAND REDUCTION, AND TO GIVE
THEM THE OPPORTUNITY TO ILLUSTRATE WHAT THEIR COUNTRIES
ARE DOING OR MIGHT DO IN THIS FIELD. THE GOAL IS, THROUGH
SUCH A CONFERENCE, TO ENCOURAGE FOREIGN HEALTH/SCIENCE
POLICY OFFICIALS TOWARD BROADER AND MORE FRUITFUL
INTERNATIONAL SCIENTIFIC COLLABORATION ON THESE SUBJECTS.

3. THE DEPARTMENT ASKS ACTION ADDRESSEES TO EXPLORE HOST
GOVERNMENTS' INTEREST IN SUCH A CONFERENCE, AND ASCERTAIN
TOPICS IN WHICH THEY WOULD BE PARTICULARLY INTERESTED.
PLEASE IDENTIFY AS POSSIBLE ATTENDEES ONE OR TWO HOST

GOVERNMENT HEALTH/SCIENCE POLICY OFFICIALS OF SUFFICIENTLY
SENIOR RANK TO MAKE DECISIONS REGARDING POSSIBLE FUTURE
PROGRAMMATIC INVOLVEMENT.

4. THE CONFERENCE PROCEEDINGS WILL BE IN ENGLISH. USG
BUDGET CONSTRAINTS OBLIGE US TO PLAN ON ATTENDEES' PAYING
THEIR OWN EXPENSES.

5. POSTS SHOULD DRAW ON THE INFORMATION IN THIS CABLE IN
APPROACHING CONTACTS. IN YOUR REPLIES, IT WOULD BE
HELPFUL TO HAVE YOUR OWN BRIEF ASSESSMENT OF HOST
GOVERNMENT CAPABILITIES AND ACTIVITIES IN BIOMEDICAL
RESEARCH RELATED TO DRUG ADDICTION.

BACKGROUND

6. THIS CONFERENCE WILL ADVANCE THE GOALS OF THE
PRESIDENT'S NATIONAL DRUG STRATEGY, WHICH EMBRACES BOTH
SUPPLY-SIDE EFFORTS AND ENCOURAGEMENT OF A MULTINATIONAL
APPROACH IN DEMAND REDUCTION. ONE ELEMENT OF DEMAND
REDUCTION IS NEUROSCIENTIFIC RESEARCH, I.E., STUDIES OF
PHYSIOLOGICAL CAUSES OF DRUG ADDICTION, EFFECTS OF
ADDICTION, AND TREATMENT OF THE DISORDER BY
PHARMACOLOGICAL MEANS. TO DATE THERE SEEMS TO HAVE BEEN
LITTLE SYSTEMATIC INTERGOVERNMENTAL RPT INTERGOVERNMENTAL
EXCHANGE OF PERTINENT DATA AND PROFESSIONAL ACTIVITIES IN
THESE AREAS. (THERE HAVE BEEN SCIENTIST-TO-SCIENTIST
EXCHANGES, WHICH CONTINUE, BUT LITTLE BETWEEN GOVERNMENTS
CONCERNING INTERNATIONAL COLLABORATION.)

7. THE U.S. PERFORMS THE MAJORITY OF THE WORLD'S DIRECTED
RESEARCH IN THE SUBJECT AREAS. THE CONFERENCE WILL
PROVIDE AN EDUCATIVE FORUM AND SYNOPSIS OF U.S.
PROGRAMMATIC EFFORTS, AFFORD OPPORTUNITY TO SURVEY RELATED
FOREIGN PROGRAMS, AND HOPEFULLY IDENTIFY RESEARCH AREAS
FOR MUTUALLY BENEFICIAL SCIENTIFIC COOPERATION. A
PUBLICATION OF PROCEEDINGS OF THE CONFERENCE IS
ANTICIPATED.

8. THE NATIONAL INSTITUTE FOR DRUG ABUSE (A COMPONENT OF
THE DEPARTMENT OF HEALTH AND HUMAN SERVICES) HAS AGREED TO
ARRANGE AND HOST THIS INTERNATIONAL CONFERENCE IN

UNCLASSIFIED

UNCLASSIFIED
Department of State

OUTGOING
TELEGRAM

PAGE 02 OF 02 STATE 066888 012258Z

SHB9409

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SHB9409

WASHINGTON, MOST LIKELY AT THE NATIONAL INSTITUTES OF HEALTH CAMPUS IN BETHESDA, MARYLAND), TO: A) REVIEW CURRENT BIOMEDICAL RESEARCH ON DRUG DEMAND REDUCTION, ADDICTION, AND ADDICTION CURTAILMENT; B) ASCERTAIN WHAT OTHER COUNTRIES ARE DOING OR MIGHT DO IN THIS FIELD AND TO IDENTIFY SUITABLE AREAS FOR COLLABORATION; AND C) HELP ESTABLISH CONTACTS BETWEEN FOREIGN SCIENCE-POLICY LEVEL OFFICIALS AND U.S. SCIENTISTS AND COUNTERPARTS, TOWARD POSSIBLE CONCLUSION OF RELEVANT INTERNATIONAL COOPERATIVE AGREEMENTS.

SUBJECT PARAMETERS

9. THE SUBJECT MATERIAL ENCOMPASSES POSSIBLE COLLABORATIVE PROJECTS IN THE FIELD OF BIOMEDICAL AND PHARMACOLOGICAL RESEARCH RELATING TO ILLICIT DRUG USE, ITS

TREATMENT AND PREVENTION. FOR THE PURPOSES OF THIS CONFERENCE, "SUBSTANCE ABUSE" MEANS ADDICTION TO CONTROLLED (UN-DEFINED) SUBSTANCES - E.G., COCAINE, HEROIN, AND PSYCHOTROPIC SUBSTANCES. THE CONFERENCE IS NOT INTENDED TO FOCUS ON LEGAL, SOCIAL OR BEHAVIORAL ASPECTS OF THE PROBLEM, BUT RATHER ITS PHYSIOLOGICAL ASPECTS.

INVITEE DESIDERATA

10. TO MAXIMIZE THE EFFECTIVENESS OF EXPOSING U.S. PROGRAMS, THE "STATE OF THE ART" AND POTENTIAL FOR COLLABORATION, WE NEED TO INVITE HOST GOVERNMENT OFFICIALS WITH RESPONSIBILITY FOR POLICY AND FUNDING DECISIONS. THEREFORE, POSTS SHOULD TARGET RELEVANT SENIOR POLICY OFFICIALS WITH AN INTEREST IN HEALTH. ALTERNATIVELY, INVITEES MIGHT BE DIRECTORS OF NATIONAL INSTITUTES OF HEALTH, FOR EXAMPLE, COUNTERPARTS OF THE U.S. HEAD OF THE NATIONAL INSTITUTE FOR DRUG ABUSE AND THE DEPUTY DIRECTOR FOR DEMAND REDUCTION OF THE U.S. OFFICE OF NATIONAL DRUG CONTROL POLICY (ONDCP). IF THE GOVERNMENT OFFICIALS WHO WOULD COME ARE NOT THEMSELVES SCIENTIFICALLY CONVERSANT, THEY SHOULD BE ACCOMPANIED BY AN ADVISOR WHO IS (NOTE THAT WE ARE CONTEMPLATING A SMALL CONFERENCE, WITH TOTAL FOREIGN PARTICIPANTS TO NUMBER AROUND 50 PERSONS.)

11. FOLLOWING IS A NOTIONAL CONFERENCE AGENDA WHICH YOU MAY SHAPE WITH HOST CONTACTS AND ON WHICH YOU SHOULD ASK

THEIR SUGGESTIONS (A FINAL AGENDA WOULD BE CIRCULATED BEFORE THE CONFERENCE). POSTS SHOULD EMPHASIZE THAT THE MAIN THEME AND GOAL OF THIS MEETING IS ENHANCED INTERNATIONAL SCIENTIFIC INFORMATION EXCHANGE AND COLLABORATION, AND THIS WILL UNDERLIE ALL THE MEETING SEGMENTS. WE WOULD HOPE TO SEE THIS CONFERENCE PRODUCE RECOMMENDATIONS ON FUTURE COLLABORATION. POSTS SHOULD CONVEY, THEREFORE, THAT INVITEES SHOULD BE PREPARED TO DISCUSS THEIR COUNTRIES' ACTIVITIES AND/OR INTEREST AND POSSIBLE ACTIVITIES IN THIS FIELD. DEPARTMENT WILL PROVIDE POSTS WITH ADDITIONAL DETAILS ON THE AGENDA (E.G. SPECIFIC SPEAKERS) AS SOON AS POSSIBLE. NONETHELESS, WE ENCOURAGE INITIAL INDICATIONS OF HOST COUNTRY INTEREST PENDING MORE DETAILED CONFERENCE INFORMATION.

SESSION I: OPENING REMARKS

A) APPROACHES TO DEMAND REDUCTION AND THE ROLE OF SCIENTIFIC RESEARCH

B) MULTI-NATIONAL RESPONSES TO DRUG DEMAND

SESSION II: NEURAL BASIS FOR DRUG ADDICTION

A) OPIATES

B) COCAINE

C) OTHER DRUGS OF ABUSE

SESSION III: PHARMACOLOGICAL TREATMENTS FOR DRUG ADDICTION

A) PHARMACOLOGICAL INTERVENTIONS TO TREAT DRUG ABUSE: THEORETICAL POSSIBILITIES

B) FEASIBILITY OF DEVELOPING EFFECTIVE PHARMACOLOGICAL INTERVENTIONS FOR ALL ASPECTS OF DRUG ABUSE, E.G. CRAVING, RELAPSE, ETC.

C) CURRENT PHARMACOTHERAPIES AND THEIR EFFICACY

SESSION IV: MODERN SCIENTIFIC APPROACHES FOR STUDYING DRUG ABUSE

A) FOR EXAMPLE, THE USE OF IMAGING TECHNIQUES FOR UNDERSTANDING THE EFFECTS OF DRUGS OF ABUSE ON THE BRAIN AND MOLECULAR BIOLOGICAL APPROACHES TO UNDERSTANDING THE GENETIC LINK TO DRUG SEEKING BEHAVIOR AND THE VULNERABILITY TO ADDICTION

SESSION V: FIELD SITE VISITS

SESSION VI: CLOSING SESSION

12. FOR TOKYO: DURING FEBRUARY 13-15 ESCAP CONFERENCE, DEPUTY DIRECTOR OF HEALTH MINISTRY'S NARCOTICS DIVISION KAZUO KIMURA SUGGESTED THE CONVENING OF A REGIONAL CONFERENCE ON SCIENCE RESEARCH IN DRUG ABUSE REHABILITATION, PERHAPS ORGANIZED COLLABORATIVELY BY ESCAP AND WHO. EMBASSY SHOULD NOTE TO GOJ CONTACTS THAT PROPOSED ESC CONFERENCE MAY PARTIALLY MEET GOJ'S INTEREST IN SCIENCE-BASED INFORMATION EXCHANGE IN DEMAND REDUCTION

AREA.

13. REPLIES, INCLUDE NO NEGATIVE REPLIES, REQUESTED BY MARCH 22, 1991. PLEASE SLUG REPLIES ALSO FOR DES/SC. M. QUEAR.
BAKER

UNCLASSIFIED

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

June 19, 1991

May

MEMORANDUM FOR ALLAN BROMLEY

FROM:


D.A. HENDERSON

SUBJECT:

CONFERENCE ON BIOMEDICAL APPROACH TO ILLICIT
DRUG DEMAND REDUCTION

The concept of an international conference on this topic is both sound and timely. In my view, the attack on the drug problem has been overbalanced toward interdiction with far too little devoted to diminishing demand and pathetically little directed toward needed basic science to understand, to treat and perhaps to prevent addiction. The international conference described will go far, I believe, in awakening substantially greater interest in this area.

This conference is one I have supported and encouraged. It will not provide a "quick fix" but it should help in laying a needed foundation for future research.

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION

DOCUMENT NUMBER: 9120824

FROM: LYSENKO, Paul D. and Natalie

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 03/18/91

SUBJECT: INFORMATION ON ASBESTOS.

ASSIGNED TO:

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO: Life Sciences

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 03/21/91

FILE: P-LIFE SCIENCES

1 To: Adviser to U.S. President FOR Technology
and Science DR. Allan Bromley
2 Dear Dr. Bromley,
3 We think this article will be
4 helpful to know the truth about
5 the asbestos.

6 Thank you very much.

7 Sincerely,

8 Paul and Natalie Lysenko
March 18th, 1991

Paul D. Lysenko, Chemist

9120824

Natalie Lysenko, Chemist

214 Hungerford Street

Pittsfield, Mass. 01201

March 18th, 1991

91 MAR 21 AIO : 19

OFFICE OF THE
DIRECTOR

9 The asbestos ready made products are not losing their fibers into the air and are thus not dangerous.

10
11
12 In the USA for the last 80 years are deposited 30 million tons of the ready asbestos products. E.P.A. -
13 Enviromental Protection Agency affirms that 30 million tons of the ready asbestos products are losing
14 into the air their fibers which can cause a cancer. In January 1986 the E.P.A. proposed to ban and throw
15 away whole the asbestos from the buildings for the next ten years. At that time, 1986 and 1987, we sent
16 to many Senators and Representatives, President of USA, US Consumer Product Safety Commission,
17 and the expert for the toxicology Dr. John S. Andres, M.D., and many US newspapers and magazines
18 our article "Asbestos is not guilty" with four Supplements, and the article: "The asbestos products are
19 safe, not toxic. U.S.A. schools buildings need the asbestos products". In this article is shown, that the
20 asbestos ceilings are not losing their fibers into the air, the pipe's asbestos insulation do not lose their
21 fibers into the air, the asbestos roof tiles also do not lose their fibers into the air. The roof shingles
22 painted with tar containing the asbestos fibers are protecting the air against the emission from shingles
23 the tar particles which are causing a cancer.

24
25 The pipes made of the cement with asbestos fibers are strong and are less emitting into water the small
26 particles of the cement.

27
28 In January 1986 the permissible standard accepted by E.P.A. was two million asbestos fibers in one
29 cubic meter of air. In June 1986 after we sent our articles, this permissible standard was reduced 20
30 times that is to say it is 100,000 fibers in cubic meter of the air what is corresponding to 100 mg. asbes-
31 tos fibers in the air of the 100 cubic meter air-room. Because the asbestos is 2.5 times heavier the water

32 and its fibers are intertwined they fall down quickly from the room ceiling to its floor, and for 6
33 minutes they all will be on the floor. During ten years the asbestos ceiling (weight 86 Kg.) fall down to
34 the floor about 86 kg. what means that the asbestos ceiling is disappeared. In reality no one of the as-
35 bestos ceiling has disappeared in spite of its age. In this same room instead an asbestos ceiling (weight
36 86 kg.) to hang the asbestos roofing felts or the asbestos paper, weight of which is about 5 kg. As every
37 6 minutes fall down to the floor 100 mg. asbestos it means for seven months all the asbestos felts or as-
38 bestos paper will disappear. In reality it stays not changed by weight. Everybody, who has in their
39 house the old asbestos, can see that this asbestos by weight is not changed. The pipes covered with as-
40 bestos insulation do not lose their weight with age. Even during fire they stay unchanged. On contrary
41 the substitutes of the pipes asbestos insulation during fire are very quickly changed into soot and gases,
42 and pipes have been damaged by fire.

43
44 To be completely sure that the asbestos which is existing in a building does not supply the air by its
45 fibers, to conduct the following experiments. To pass through vacuum-cleaners the air inside and out-
46 side of the building having the asbestos. The content of the vacuum-cleaners will be sand, clay dust,
47 and vegetation fibers but not the asbestos fibers. In case under a microscope is difficult to differ the as-
48 bestos fibers from vegetation fibers the chemical analysis can help. About this is in our article.

49
50 We think now is time for Congress to stop to ban the asbestos from buildings and to permit to use the
51 asbestos at construction of new buildings. Also we think now is possible not to be against the publica-
52 tions of our six articles about asbestos.

53
54 Long time ago in Massachusetts was "catching" the witches. Now also in Massachusetts appear Paul
55 and Natalie Lysenko, two chemists, who categorically are standing against the catching of witches in
56 whole the USA. The catching in the air the asbestos fibers which are not existing in the USA buildings
57 having the ready asbestos products is the same. The outer air also does not content the asbestos fibers.
58 Long time ago because of the Massachusetts witches the people did not die but the modern witches -
59 asbestos fibers, which are not existing in the air, "cause" many thousand deaths from cancer.

60
61 By this reason the asbestos persecutors are stopping the publication of the truth about wisely chosen and
62 widely applied in USA useful chrysotile asbestos.

63 For the satellite-telescope is spent about 1.5 billion dollars. It has been provided widely the criticism
64 about the failures in its construction. At such complicated problem is normal that the mistakes are in-
65 evitable.

66
67 At the ban of very useful, not dangerous the ready asbestos products from the USA buildings is spent
68 and has been spent till now the money about one hundred times more (150 billion dollars) than for the
69 creation of the satellite-telescope. And about this all are silent and even more - is prohibited the publi-
70 cation of our articles about the asbestos.

71
72 *Paul Lysenko*

Paul Lysenko

73
74
75 *Natalie Lysenko*

Natalie Lysenko

"CORRESPONDENCE TRACKING"

TYPE: Action Item

DOCUMENT NUMBER: 9120898

FROM: LANNAK, Fred & Jeanne; Newark, DE

TO: DAB

DATE OF
CORRESPONDENCE: 03/17/91

SUBJECT: Scoliosis Research and Lack of Cooperation with NIH

ASSIGNED TO: Rachel Levinson

ACTION REQUIRED: Necessary Action

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED: 03/27/91

COPIES TO:

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS: Rachel answered their 02/13/91 request and referred them to Dr. James Mason at DHHS. Nothing further is necessary from OSTP.

DATE RECEIVED: 03/25/91
DATE RECEIVED DLS: 03/27/91

FILE: ~~DLS~~
P- Life Sciences

2.13

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

February 13, 1991

Dear Drs. Lannak:

As the Assistant Director for Life Sciences, Dr. Bromley has asked me to respond to your January 29 letter regarding the difficulties you have encountered with the research grant application process at the National Institutes of Health. The Office of Science and Technology Policy (OSTP) does not conduct or support research. It is the mission of the Office of Science and Technology Policy is to provide the President and the White House with the best scientifically-based advice on policy decisions.

As the attachment to your letter shows, the National Institutes of Health is part of the Public Health Service (PHS) in the Department of Health and Human Services. The head of PHS is Dr. James O. Mason, and I suggest that you contact him directly. His mailing address is Dr. James O. Mason, Assistant Secretary for Health, Department of Health and Human Services, Room 716G, Hubert Humphrey Building, 200 Independence Avenue, S.W., Washington, D.C. 20201.

Sincerely yours,



Rachel E. Levinson
Assistant Director
for
Life Sciences

Dr. Fred Lannak
Dr. Jeanne Lannak
206 Mederia Circle
Newark, Delaware 19702

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TYPE: Action Item

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OSTP DUE DATE:

DATE COMPLETED: 03/27/91

COPIES TO:

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS: Rachel answered their 02/13/91 request and referred them to Dr. James Mason at DHHS. Nothing further is necessary from OSTP.

(copy attached)

DATE RECEIVED: 03/25/91
DATE RECEIVED DLS: 03/27/91

FILE: DLS

Life Sciences

**EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506**

February 13, 1991

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Sincerely yours,



**Rachel E. Levinson
Assistant Director
for
Life Sciences**

**Dr. Fred Lannak
Dr. Jeanne Lannak
206 Mederia Circle
Newark, Delaware 19702**

9120898

A SCIENTIFIC ANALYSIS OF A SCOLIOSIS

By Drs. Fred and Jeanne Lannak

March 17, 1991 RECEIVED

D. Allan Bromley
Assistant to the President
1600 Pennsylvania Avenue, N.W.
Washington, D.C. 20500

91 MAR 25 AM: 20

Dear D. Allan Bromley:

OFFICE OF THE
DIRECTOR

This letter is being given to the same 31 members of President Bush's Executive Branch that we sent our previous letters to on January 29, 1991. Our previous letters included President Bush, Vice President Dan Quayle, all the Cabinet Members of President Bush, Max Marlin Fitzwater and other important officials in the President's Executive Branch.

Our previous letter asked for assistance with finding someone at the National Institutes of Health (NIH) to communicate with about Scoliosis Research (curved spinal column research) that we have been conducting for over two decades. We explained that our last 12 years of trying to communicate with the NIH about our Scoliosis Research has kept us running around in a giant circle that got us nowhere.

The replies that we received from the 31 members of President Bush's Executive Branch from our January 29, 1991 letters were very courteous. The replies appeared to be directed toward helping us with our Scoliosis Research communication problem at the NIH.

The replies that we received from the Department of Health and Human Services (HHS) concerning the 31 letters that we sent to the President's Executive Branch were altogether different. The letters we received from HHS indicated that an investigation into the operations of NIH is needed. Something is going on at the NIH that is not completely honest. Thirty eight percent of all the taxpayers money the Federal Government spends is used by HHS.

Letters we received from Steven J. Hausman, Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases and Stephen L. Gordon, Musculoskeletal Diseases Program Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases told us to get lost with our Scoliosis Research in a sweet and tactful manner. They sent us on wild goose chases to places and organizations that they already know are nothing more than wild goose chases.

President Bush showed Americans during the Iraqi/Kuwaiti war, things that look good on the outside may be altogether rotten on the inside. The NIH have bounced us around like a couple of rubber balls just because we asked them to help us with our Scoliosis Research.

Your concern in this matter is appreciated.

Sincerely yours,

F. J. Lannak

J. Lannak

Dr. Fred Lannak & Dr. Jeanne Lannak
206 Mederia Circle
Newark, DE 19702

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION

DOCUMENT NUMBER: 9121022

FROM: LESHNER, Alan I.: DEPARTMENT OF HEALTH & HUMAN SERVICES

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 04/04/91

SUBJECT: A THANK YOU FOR YOUR PARTICIPATION AT THE FIRST
DECADE OF THE BRAIN SYMPOSIUM.

ASSIGNED TO:

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS: Photograph enclosed.

DATE RECEIVED: 04/08/91

FILE: LIFE SCIENCES



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
RECEIVED

9121022
91 APR 9 10 49
Alcohol, Drug Abuse, and
Mental Health Administration
Rockville MD 20857

April 4, 1991

OFFICE OF THE
DIRECTOR

The Honorable Allan Bromley
Assistant to the President
for Science and Technology
Old Executive Office Building
17th Street and Pennsylvania Avenue, N.W.
Washington, D.C. 20506

Dear Dr. Bromley:

Thank you again for your participation at the first Decade of the Brain Symposium held at the National Academy of Sciences in July, 1990.

I would like to share this photo with you taken at this important event which formally recognized the start of the 1990's as the "Decade of the Brain". You will be pleased to know that the book will be published later this year.

I look forward to the continued activities of this important event over the next decade and hope to see you again soon.

Sincerely,

Alan I. Leshner, Ph.D.
Acting Director
National Institute of Mental Health

Enclosure



"CORRESPONDENCE TRACKING"

TYPE: ACTION

DOCUMENT NUMBER: 9120785

FROM: PESCHEL, Enid: YALE UNIVERSITY SCHOOL OF MEDICINE

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 03/15/91

SUBJECT: BIOLOGICALLY-BASED BRAIN DISEASE IN CHILDREN AND
ADOLESCENTS

ASSIGNED TO: Life Sciences

ACTION REQUIRED: FOR DAB SIGNATURE

SENDER'S DUE DATE:

OSTP DUE DATE: 04/01/91

DATE COMPLETED: -----

COPIES TO: D. Allan Bromley
Maryanne Bach

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 03/18/91

FILE: **LIFE SCIENCES**

9120785

YALE UNIVERSITY
THE SCHOOL OF MEDICINE

Howard Spiro
Program Director

Enid Peschel
Co-Director

Kenneth Kashkin
Assistant Director

Nance Cunningham
Program Coordinator

Priscilla W. Norton
Volunteer

Eric Krakauer, YMS
Student Coordinator

Advisory Board

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Robert Jay Lifton
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Robert J. Levine
Bernard Lytton
Harvey N. Mandell
Marjorie Mandell
Laura Manuelidis
Alan C. Mermann
Saul C. Milles
David F. Musto
Lisa Newton
Sherwin B. Nuland
William B. Ober
Cynthia Ozick
Richard E. Peschel
Kyle D. Pruett
Richard M. Ratzan
Frederick P. Rose
Richard Selzer
Richard B. Sewall
John E. Smith
William C. Summers
Alan Trachtenberg
John H. Warner
Eleanor Clark Warren
Robin W. Winks



RECEIVED

91 MAR 18

MAILING ADDRESS:

8 Country Club Drive
Woodbridge, Connecticut 06525
March 15, 1991

THE PROGRAM FOR HUMANITIES
IN MEDICINE

P.O. BOX 3333
333 CEDAR STREET, 294 YPB
NEW HAVEN, CONNECTICUT 06510
TELEPHONE (203) 785-3494
FAX (203) 785-7273

397-9269

D. Allan Bromley, Ph.D.
Assistant to the President for Science and Technology
The White House
Washington, D.C. 20506

Dear Allan:

Thank you for having sent a copy of my letter with Klerman's article to Roger Porter, M.D., Deputy Director of the National Institute of Neurological Disorders and Stroke (NINDS). By the rights of science, NINDS (and not the absurdly-named National Institute of "Mental Health") should logically be the center for the scientific study and treatment of biologically-based brain diseases (BBBD) such as schizophrenia, bipolar and unipolar disorders, autism, pervasive developmental disorder, obsessive-compulsive disorder, Tourette's disorder, anxiety and panic disorders, attention deficit disorder, hyperactivity, attention deficit hyperactivity disorder.

I am enclosing two things for you:

- 1) Our most recent article, "A Medical Model for Specialists in Biologically-Based Brain Disease" (Perceptual and Motor Skills, 1991)
- 2) An outstanding chapter by Roland Ciaranello, M.D., "The Neurobiology of Developmental Disorders," that scientifically explains how BBBD are neurobiological disorders which, like other neurological disorders (e.g. mental retardation, etc.) are biologically-caused

I wonder: Could some of the "Decade of the Brain" activities fund a national conference that I would help organize on BIOLOGICALLY-BASED BRAIN DISEASE IN CHILDREN AND ADOLESCENTS? For our book *Biologically-Based Brain Disease in Children and Adolescents* we have 15 top neuroscience and basic science researchers writing in non-technical language about various BBBD. I would love to

get many of these scientists together for a conference that would discuss their research and would also translate their scientific findings into non-technical language. It is absolutely essential for these scientists to educate the public about the biological nature of these neurobiological disorders. Most of the country--including lay persons and "mental health" professionals--remains entrapped in the antiquated notions promulgated by decades of non-scientific psychobabble. One of the priorities of the Decade of the Brain should be to try to educate this country about the importance of basic science and neuroscience research. The brain and BBBD, at last, are becoming objects of scientific inquiry. Without science, medicine is no better than witchcraft.

We appreciate your interest in trying to ground psychiatry in science, evidence and efficacy, instead of on mere theory, opinion and belief. Dick joins me in sending you our warmest good wishes.

Sincerely,

A handwritten signature in dark ink, appearing to read "Enid", with a long, sweeping horizontal line extending to the right.

Enid Peschel, Ph.D.

Co-Director, Program for Humanities in Medicine

Assistant Professor (Adjunct), Department of Internal Medicine

Yale University School of Medicine

PHONE: (203)-397-9269

A MEDICAL MODEL FOR SPECIALISTS IN BIOLOGICALLY-BASED BRAIN DISEASE¹

RICHARD PESCHEL AND ENID PESCHEL

Department of Therapeutic Radiology
Department of Internal Medicine
Yale University School of Medicine

Summary.—This response to Spiegel's comments on our proposal for a new medical specialty emphasizes the need for a residency designed to provide training in evaluation and treatment of patients with biologically-based brain disease.

In his critique of Peschel and Peschel (10), Spiegel (13) objects to our proposal for a new medical specialty in biologically-based brain diseases (BBBD), e.g., schizophrenia, bipolar and unipolar disorders, autism, pervasive developmental disorder, obsessive-compulsive disorder, Tourette's disorder, anxiety and panic disorders, etc. Spiegel quite rightly states that psychiatrists are already being trained in the biologically-based sciences. However, our proposal is to create a group of BBBD professionals who will: (a) specifically direct 100% of their research time and clinical efforts to the treatment of severe mental illness (BBBD) and not to "mental health" problems and (b) establish treatment programs for BBBD that are based only on rigorous clinical trials and scientific data. BBBD must be distinguished from mental health problems such as those caused by abuse, neglect, crime, poverty, emotional, neurotic, or life-adjustment issues.

Our emphasis on the neurobiochemical model of BBBD and the need for BBBD specialists is based on two points. (a) For the first time ever, the *revolution* occurring in molecular biology and neurobiology is identifying reproducible, scientifically-verifiable abnormalities in brain chemistry, anatomy, and function that help explain BBBD (2, 5, 7, 14). (b) Scientific clinical trials have proved the efficacy of many psychotropic drugs that have relieved the agony of millions of people with BBBD (1, 6, 11, 12). Calling for a medical specialty in BBBD should not be viewed merely as an historical oscillation "between the dominance of genetic/biochemical and psychotherapeutic aspects of psychiatry." Rather, our proposal comes from sound scientific progress in the fundamental understanding of BBBD, which are serious, chronic, often catastrophic neurobiological diseases characterized by brain malfunctions and/or malformations (7).

Spiegel states that "a major experiment in what the authors propose was

undertaken some years ago at the University of California in San Francisco, where a Doctor of Mental Health program was undertaken." We are not proposing a "mental health" program of any kind, nor are we proposing a six-year postbachelor's degree program like the one used in California. We are proposing a post-M.D. residency program that concentrates on producing physician-scientists specializing only in BBBD. Patients with a BBBD—like patients with multiple sclerosis, diabetes or heart disease—have a right to be treated by a physician who is a specialist in their particular disease.

According to Spiegel, a BBBD specialty would be "a redundancy" because, he says, "we are already training professionals in the biological basis of mental illness. They are called psychiatrists." However, it is not enough just to train professionals in the biological basis of "mental" illness. Unfortunately, many psychiatrists trained under existing programs refuse to treat patients with BBBD (15); many do not prescribe, or are not expert in using, psychotropic medications, despite their documented efficacy for BBBD (6). Many psychiatric training programs still teach nonscientific approaches (psychoanalysis) and psychodynamic modalities as though they were equal in importance to scientifically-based therapies (3). BBBD specialists would treat only patients with BBBD, would be experts in psychopharmacology and, to evaluate the efficacy of a treatment, would use only scientific data either from prospective clinical trials or from long-term retrospective studies.

We agree with Spiegel that all "biologically based illnesses have psychosocial consequences and are susceptible to psychosocial intervention." Using carefully designed clinical trials, specialists in BBBD could scientifically establish which psychosocial interventions are actually efficacious for BBBD patients.

Spiegel said that support by the National Alliance for the Mentally Ill (NAMI) for a BBBD specialty is due to "the now discredited theory that schizophrenia is caused by dysfunctional family interactions." This statement is only partially right because NAMI and its activities are not confined to schizophrenia alone. NAMI's 130,000 members include families caring for persons with many kinds of BBBD (not just schizophrenia), consumers, and psychiatric professionals (8). NAMI advocates for all persons with mental illness and for more federal funding for science research focused on uncovering the neurobiological mechanisms of BBBD (4). With the National Mental Health Association and the National Depression and Manic-Depressive Association, NAMI members founded—and help support—the National Alliance for Research on Schizophrenia and Depression (NARSAD) (9).

This is the Decade of the Brain and the era of the neuroscientific revolution. To use new information effectively constructive work together by the psychiatric profession, other health professionals, advocacy groups, govern-

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ment agencies, educators, and so on is needed for a critical reevaluation of how and by what kinds of specialists people with BBBD would best be treated. It is time for a new generation of physician-scientists interested in BBBD to specialize in these devastating neurobiological diseases and to work together to evaluate with rigorous scientific clinical trials all forms of therapy and interventions for BBBD.

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NAMI-CAN

copy

expressly for *Children and Adolescents*

MAILING ADDRESS:

8 Country Club Drive
Woodbridge, Connecticut 06525
March 15, 1991

Roger J. Porter, M.D., Deputy Director
Department of Health and Human Services
National Institutes of Health
National Institute of Neurological Disorders & Stroke
Building 31, Room 8A52
Bethesda, Maryland 20892

Dear Dr. Porter:

Thank you for your letter of February 25 in response to my letter to Allan Bromley, Ph.D., Assistant to the President for Science and Technology. I look forward to receiving the report of your Subcommittee on Brain and Behavioral Sciences entitled "Maximizing Human Potential: The Decade of the Brain."

It was good of you to send my material to Alan Leshner, Ph.D., Acting Director of the National Institute of "Mental Health." I have been in touch with Alan for some time. He is refreshingly on the scientific wavelength. I wish that all people at the NI"MH" were as scientifically enlightened as he. A while ago, he sent me some slides documenting brain malformations and/or malfunctions in people with various biologically-based brain diseases (BBBD) called "mental" illness: autism, schizophrenia, obsessive-compulsive disorder, anxiety and panic disorders. I use these slides in lectures that I give all over the country.

I shall look for your book Controlled Clinical Trials in Neurological Disease in the Yale Medical Library. That is precisely what is needed in, but has been deplorably absent from, psychiatry, particularly in the treatment of BBBD--including, for instance, schizophrenia, bipolar and unipolar disorders, autism, pervasive developmental disorder, obsessive-compulsive disorder, Tourette's disorder, anxiety and panic disorders, attention deficit disorder, hyperactivity, and attention deficit hyperactivity disorder. These are all neurobiological disorders which, like other neurological disorders (e.g. mental retardation, multiple sclerosis, epilepsy, Parkinson's disease, Alzheimer's disease, etc.) are biologically-caused. In this regard, I am enclosing a copy of a first-rate chapter by R. Ciaranello, M.D., "The Neurobiology of Developmental Disorders."

NATIONAL ALLIANCE FOR THE MENTALLY ILL

2101 WILSON BOULEVARD, SUITE 302 • ARLINGTON, VA 22201
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In the writing that I do with my husband Richard Peschel, M.D., Ph.D. of Yale University School of Medicine, we differentiate between (a) BBBD, which are biologically-caused illnesses, and (b) "mental health" or psychological problems, which are sociologically- or environmentally-caused issues (e.g. abuse, neglect, crime, poverty; emotional, neurotic, psychological, or life-adjustment concerns). So that you can see some of our work about the need to base treatment for BBBD on science, evidence and efficacy, instead on mere theory, opinion and belief, I am enclosing 2 of our articles, plus a copy of **NAMI CAN NEWS**, which I edit.

You may be interested that ***Biologically-Based Brain Disease in Children and Adolescents***, the book that my husband and I are collecting and editing in collaboration with James and Carol Howe of the National Alliance for the Mentally Ill (NAMI), will be published early in 1992. It will begin with chapters by some of the leading neuroscience researchers in child and adolescent psychiatry writing in non-technical language about the biological underpinnings of these BBBD. There will be one chapter on each brain disease. Among the neuroscientists writing chapters for our book are **Fred Goodwin** of ADA "MH" A, **Jim Leckman** of Yale, **Joseph Coyle** of Johns Hopkins (on mental retardation); **Roland Ciaranello** of Stanford, **Judy Rapoport**, **Elliot Gershon**, and **Daniel Weinberger** of the NI "MH."

Of course, BBBD really belong in the realm of the National Institute of Neurological Disorders and Stroke (NINDS) because BBBD are biological--and not "mental" or "mental health"--problems. Do you have any researchers in NINDS who are working on these biologically-based brain diseases?

With appreciation for your interest in our work and for your devotion to science in medicine,

Sincerely,

A handwritten signature in dark ink, reading "Enid Peschel", followed by a long horizontal line extending to the right.

Enid Peschel, Ph.D.
Co-Director, Program for Humanities in Medicine
Assistant Professor (Adjunct), Dept. of Internal Medicine
Yale University School of Medicine
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cc: D. Allan Bromley, OSTP

1 *The Neurobiology of Developmental Disorders*

JOHN L. R. RUBENSTEIN, LINDA LOTSPEICH, AND
ROLAND D. CIARANELLO

From: ADVANCES IN CLINICAL CHILD PSYCHOLOGY, VOL. 13
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1. Introduction

Developmental disorders affecting intelligence and behavior are among the most mystifying diseases of humankind. This is because they are primarily caused by abnormalities in the development of the most complex human organ, the brain. Perhaps the reason so little is understood about mental retardation, autism, childhood schizophrenia, attention deficit disorder, specific learning disorders, and Tourette disorder is that very little is still understood about how a normal brain develops. The premise of this chapter is that the key to understand these illnesses is an understanding of the processes involved in neurodevelopment.

In the first section, we describe the basic processes involved in brain development. This discussion serves as a foundation for the next section, in which we review the major pathological disorders of the developing nervous system. In the final section, we examine the biological basis for the syndrome of autism. We have chosen to focus on autism because its etiology is clearly biologically based, and because of a series of recent neuropathological findings that are providing some clues about the neurobiological basis of this disorder.

2. Neurobiology of Brain Development

This section describes how the brain is assembled during the development of a mammalian embryo. Some of what is described are results from animals other than humans; however, to date, there is no reason to

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TABLE 1
Chronology of Human Brain Development

Time of gestation	Anatomical structure
15 days	Primitive streak is present.
16 days	Notochord is present.
18-21 days	Neural plate is present.
20 days	Somites begin to form, and neural folds begin to fuse.
	Neural crest forms at the site of neural fold fusion.
	Neural tube made up of a roof plate, a floor plate, and two alar and two base plates.
22 days	Optic grooves and otic placode are present.
24 days	Rostral neuropore closes.
26 days	Caudal neuropore closes.
28 days	Formation of forebrain, midbrain, and hindbrain vesicles.
32 days	Spinal ganglia are present.
33 days	Optic cup and otocyst are present.
35 days	Thalamic anlage is present.
	Forebrain divides into telencephalon and diencephalon.
	Hindbrain divides into metencephalon and myelencephalon.
6 weeks	Cerebellum begin to develop.
	First cerebral cortical neurons are born.
	Lateral geniculate nucleus (LGN) begins to develop.
	Pituitary develops.
	Anlage of striatum is present.
7 weeks	Primordial plexiform layer is present in the cerebral cortex.
	Ganglion cell axons reach LGN.
8 weeks	Cerebellar external granular layer begins to form.
	Lips begin to move reflexively.
10 weeks	Cerebellar Purkinje cell layer forms.
	Intrahemispheric commissures begin to form.
11 weeks	Longitudinal sulcus present.
	Layers 7, 1, and undifferentiated cortical plate present in cerebral cortex.
12 weeks	Amygdala nuclei are present.
	Myelination begins in the spinal cord.
	Swallowing reflex present.
15-16 weeks	Layers 7, 6, 5, 1, and undifferentiated cortical plate present in cerebral cortex.
18-20 weeks	Layers 7, 6, 5, 4, 1, and undifferentiated cortical plate present in cerebral cortex.
	LGN layers are present.
	Central sulcus present.
24-26 weeks	Layers 7, 6, 5, 4, 3c, 1, and undifferentiated cortical plate present in cerebral cortex.
	Sucking reflex present.

TABLE 1
Continued

Time of gestation	Anatomical structure
26 weeks	Central sulcus and lateral fissure are present.
28-30 weeks	Layers 7, 6, 5, 4, 3c, 3b, 1, and undifferentiated cortical plate present in cerebral cortex.
26-34 weeks	Formation of dendritic spines and branches on the pyramidal cells of the visual cortex.
38-40 weeks	Layers 7, 6, 5, 4, 3, 2b, 1, and undifferentiated cortical plate present in cerebral cortex.
Third trimester and postnatally	Synaptic maturation, granule cell migration, and axon myelination.

suggest that the basic mechanisms needed to construct a brain are not general to all higher organisms. We relate the various stages in brain development to the chronology of human neurodevelopment, which is summarized in Table 1. We describe the processes involved in the segmentation of the neural tube, the migration of the primitive neurons to form the cerebral and cerebellar cortices, axon pathway formation, cell-cell recognition, synapse development, and the critical periods in the assembly of functional neural networks. We also review several known human and mouse syndromes in which these various processes have failed to produce a normal brain.

We wish to emphasize that brain development is controlled by two major processes, which can be categorized as being intrinsic and extrinsic. Intrinsic development, which begins prenatally and extends into postnatal life, involves the construction of major parts of the brain independent of environmental influences. These intrinsic processes involve a complex set of biochemical and biophysical processes that are regulated genetically. Of course, intrinsic brain development can be influenced detrimentally by exposing the animal to agents, such as toxins and microorganisms, that interfere with normal development.

Extrinsic processes, which begin *in utero* and probably continue throughout the animal's life, use environmental stimuli to regulate brain development. These processes require that sensory systems of the animal be functioning. Typically, sensory systems begin to operate *in utero*; hence, environmental stimuli begin to affect brain development even before the animal is born. In contrast to the intrinsic processes, which largely construct the brain, the extrinsic processes produce the more subtle anatomical changes involved in the distribution and function of synapses. This difference in the processes will be reemphasized in the section on critical periods in development, where we will describe ex-

periments that show how environment influences postnatal brain development. In essence, intrinsic developmental processes produce an immature brain that is endowed with the necessary machinery to assimilate, process, integrate, and react to information from the environment.

2.1. Development of the Neural Tube

The initial phase in brain development is the generation of the progenitor cells of the nervous system. In humans, this occurs at about Embryonic Day 18 (E18), when the neural plate is first apparent. The neural plate is an ectodermal structure believed to be induced by the underlying mesodermal structures: the notochord and the paraxial mesoderm (see Moore, 1977, for a detailed description of the development of the embryonic nervous system). The neural plate is made up of neuroectodermal cells that are the precursors of the central nervous system. Initially, the neural plate is a flat layer of cells; however, by about E21 the plate folds up to form a tube; the anterior part of the tube will form the brain, and the posterior part will differentiate into the spinal cord. The neuroectodermal cells at the lips of the neural tube migrate laterally from the closed tube and form the neural crest. These cells then differentiate into the dorsal root ganglia, the autonomic ganglia, the adrenal medulla, and a variety of other tissues.

Closure of the neural tube creates an internal cavity called the *ventricle*. The wall of the neural tube is made up of one layer of cells, whose basal processes abut the ventricle, and whose apical processes form the tube's outer surface (the pial surface). These cells undergo a mitotic division every six hours (Morris-Kay & Tuckett, 1987). Following cell division, some cells migrate toward the pial surface. The result is the production of two layers of cells in the neural tube: the ventricular layer, which contains the mitotically active undifferentiated cells, and the cortical plate, which contains the postmitotic newly differentiated neurons.

By 28 days of gestation, the brain has expanded in size and forms three vesicular swellings: the forebrain (prosencephalon), the midbrain (mesencephalon), and the hindbrain (rhombencephalon). In the fifth week, the forebrain divides into the telencephalon and the diencephalon, and the hindbrain divides into the metencephalon and the myelencephalon. These five vesicles differentiate into the final structures of the brain. The telencephalon gives rise to the cerebral vesicles, the diencephalon forms the thalamus, the mesencephalon becomes the midbrain, the metencephalon becomes the pons and the cerebellum, and the myelencephalon differentiates into the medulla oblongata.

The spinal cord and the brain stem also undergo a structural subdivision along their dorsoventral axis into six anatomically distinct

plates of tissue that have different developmental fates (Moore, 1977). The dorsal part of the neuraxis becomes the roof plate, and the ventral surface becomes the floor plate. The dorsolateral sides are made up of two alar plates, and the ventrolateral sides are the two base plates. The alar plates differentiate into regions of the spinal cord and the brain stem involved in sensory processing, whereas the base plates differentiate into neurons involved in the motor system.

Therefore, during the earliest stages of brain development, the neural tube becomes segmentally differentiated. There is anatomical evidence that the vertebrate neural tube transiently has a segmented structure, whose anterior parts form the various elements of the brain and the brain stem, and whose posterior region gives rise to the repetitive units of the spinal cord and its associated ganglia (Lumsden & Keynes, 1989). Groups of cells, in different regions of the neural tube, then differentiate into different structures. Somehow, the cells along the neural tube know where they are. Cells situated posteriorly are programmed to form the parts of the spinal cord, whereas cells situated anteriorly develop into the various parts of the brain. It is as if there is an exact blueprint that specifies the details of this complex process.

Study of the development of the invertebrate nervous system promises to aid in the understanding of vertebrate brain development, because of the relative simplicity of the invertebrate brain, and because of a number of known mutations that disrupt normal development. In the grasshopper, the embryonic nervous system is made up of a repeating pattern of segmental ganglia, which undergo an invariant pattern of development. Each embryonic ganglion contains about 300 neurogenic ectodermal cells (Doe, Kuwada, & Goodman, 1985). These cells give rise to 60 neuroblasts, which in turn produce about 2,000 neurons. The adult neurons have a wide range of shapes and synaptic connections. Evidence from the work of Doe *et al.* (1985) suggests that both cell-lineage-dependent gene expression and the local chemical environment (as defined by cell-cell, and cell-extracellular-matrix interactions and diffusible molecules) are involved in the determination of cell lineage. In other words, a variety of intrinsic mechanisms are involved in the determination of a cell's fate. There are a number of genes, such as the *achaete-scute* gene complex and the segmentation genes, which are known to be required to orchestrate this developmental pathway (Jimenez, 1988). Deletions in the *achaete-scute* genes disrupt the embryonic nervous system, and mutations in segmentation genes (such as *fushi-тарazu* and *even-skipped*) cause the elimination of entire segments of the embryo (including its nervous system).

Some of the segmentation genes are also expressed in parts of the nervous system at later stages of development. For instance, the *fushi-*

tarazu gene also affects the axon pathway choice of a specific neuron in each segmental ganglion (Doe, Hiromi, Gehring, & Goodman, 1988). Another class of genes, called the *homeotic genes*, controls the identity of entire segments of the insect (Doe & Scott, 1988; Scott & Carroll, 1987). Mutations of these genes can lead to devastating results, such as the loss or a change in identity of a segment.

Recently, several vertebrate genes have been isolated that have DNA sequences related to the genes in *Drosophila* that regulate development. For instance, the murine oncogene *int-1*, which is related to the *Drosophila* gene *wingless*, is expressed in a subset of cells at the lateral edge of the neural plate (Shackelford & Varmus, 1987; Wilkinson, Bailes, & McMahon, 1987). Also, the POU-domain genes encode a family of proteins that are expressed in various subsets of cells in the developing and the adult mammalian nervous system (He, Treacy, Simmons, Ingraham, Swanson, & Rosenfeld, 1989). Although it has not been proved, it is likely that the development of the human nervous system is controlled by such genes. A mutation in this type of gene could have devastating effects, such as the elimination of an entire segment of the nervous system. However, a mutation that interfered with the construction of a smaller group of cells, such as part of the cerebral cortex, might result in a subtle cognitive deficit. It is a premise of this chapter that genes play a critical role in the development of the human brain, and that some forms of mental retardation and autism are due to genetic mutations.

2.2. Development of the Cerebral Cortex

As noted in the last section, the most anterior part of the neural tube is called the *telencephalon*. The dorsolateral walls of the telencephalon evaginate to form the two cerebral hemispheres during the fifth embryonic week. Each embryonic cerebral vesicle has the primordia of several important brain structures. The ventral wall of the vesicle contains the primordia of the basal ganglia, the medial wall contains the primordia of the hippocampus (archicortex), the dorsolateral wall contains the primordia of the cerebral cortex (neocortex), and the region lateral to the developing basal ganglia contains the primordia of the amygdala and the pyriform cortex (paleocortex) (Marin-Padilla, 1988). Initially, the cerebral cortex makes up only 3% of the telencephalic mass; by the time of birth, it comprises 80% of the telencephalon and about 66% of the entire brain (Rakic, 1988). The cerebral cortex is the structure that is distinctively prominent in humans (Rakic, 1988). Rakic pointed out that the surface of the neocortex is greatly expanded in humans; for instance, the surface of the human neocortex is 10 times that of a maca-

que monkey, and 1,000 times that of a hedgehog. The cortex is divided into distinct regions, each with different anatomy and function. These regions are called *cytoarchitectonic areas*. A given cytoarchitectonic area may be involved in controlling motor output, or analyzing sensory information, or integrating information converging from other areas (i.e., in Wernicke's area, auditory information is decoded into language). Some areas are unique to humans, such as Broca's area, which is involved in speech production.

The adult neocortex covers the surface of the brain. It is about 2 millimeters in thickness and over 1 square foot in surface area (Hubel, 1988). Its basic architectural motif is a six-tiered structure. Each layer subserves a different function. For instance, Layer 4 receives input from the thalamus, Layers 2 and 3 receive input from Layer 4; Layers 2, 3, and 4 send output to other cortical areas, and Layers 5 and 6 send their output to noncortical regions of the brain. Also, different layers are made up of different types of neurons, as defined by their shapes (Carpenter, 1978) and neurotransmitters (Parnavelas, Papadopoulos, & Cavanagh, 1988). Layers 2 and 3, for example, are composed of small- and medium-sized pyramidal cells, Layer 4 contains small granular stellate cells, Layer 5 is composed of medium-sized pyramidal cells, and Layer 6 consists of pyramidal and fusiform cells. The nonuniform distribution of neurotransmitters and their receptors is also well-described (see Parnavelas, Papadopoulos, & Cavanagh, 1988) but is beyond the scope of this chapter. In the next section, we describe briefly how this fantastic computer is constructed.

During the early stages of brain development, the neural tube is made up of a single layer of cells that are arranged as a pseudostratified epithelium. The neuronal progenitor cells, which are called *neuroblasts*, divide every 6 hours, rapidly increasing the thickness of the neural tube's wall. These mitoses produce neurons for different periods of time, depending on the particular region of the ventricular zone. For instance, in the rhesus monkey, cortical neurogenesis stops at E70 in the anterior cingulate cortex and at E100 in the primary visual cortex (Rakic, 1988).

The neuroblasts in the ventricular zone are divided into small clusters. The clusters are separated from each other by walls made by another type of cell called the *radial glial cell* (Rakic, 1988). These clusters are called *proliferative units* and contain 3–5 cells at early stages, and up to 12 cells later in development (Rakic, 1988). Once a neuron is formed following a mitosis of a progenitor cell, it begins to migrate from its proliferative unit in the ventricular layer toward the pial surface. The neurons stop their migration just below the pial surface of the brain. The first set of cells begin their migration during the seventh embryonic

week. These cells eventually form the subplate zone (Layer 7) and the marginal zone (Layer 1, also known as the *molecular layer*). The next set of neurons migrate to cortical Layer 6 (present by Embryonic Weeks 15–16). These neurons settle in the midst of the first cell layer, splitting the cells into the subplate zone and the marginal zone. Then, Layer 5 is formed during Embryonic Weeks 15–16. Layer 4 is present by Embryonic Week 18, Layer 3 by Embryonic Week 24, and finally Layer 2 by Embryonic Week 38. Cells found in each layer of the cortex have stopped undergoing mitosis and have begun their migration at approximately the same time. Furthermore, except for Layer 1, the oldest layers are found deepest in the cortex. This means that the cells that make up the younger layers must migrate past the older layers. For instance, the cells that make up Layer 5 must migrate past the subplate (Layer 7) and the Layer 6 cells. Also, the cortical layers in humans and monkeys are constructed largely during the first half of gestation (Rakic, 1988), in contrast to species such as the mouse and the ferret, in which the cerebral cortex continues to accumulate new cells postnatally.

There is evidence that the neurons follow "guide wires" during their migrations. The cellular processes of the radial glial cells span the width of the embryonic cortex and probably guide the migrating neurons from the ventricular zone to the developing cortex (Rakic, 1972). Rakic suggested that neurons from a given proliferative unit in the ventricular zone migrate along the same fiber(s) to form a column of clonally related cells in the mature cortex. Rakic (1988) called these vertical arrays of clonally related cells "ontogenetic columns." Each ontogenetic column spans the width of the cerebral cortex. The number of neurons in a column varies from 80 in the anterior cingulate cortex, where neurogenesis lasts about 1 month, to more than 120 in the primary visual cortex, where neurogenesis lasts almost 2 months (Rakic, 1988).

Therefore, progenitor cells in each proliferative unit give rise to a column of cells in the mature cerebral cortex. This conclusion has been confirmed in part by infecting cells in the ventricular zone with an attenuated retrovirus that contains the gene for the B-galactosidase enzyme. The infected ventricular-zone cells produced neurons that contained the B-galactosidase gene. These cells migrated to the cortex to form columns of cells that also expressed the B-galactosidase enzyme (Luskin, Pearlman, & Sanes, 1988). These experiments also confirm that a single progenitor cell in the ventricular layer can give rise to cells in all of the ventricular layers, and therefore to cells with different structures and functions.

Rakic (1988) suggested that neurons become committed to differentiating into their mature phenotype soon after they are born, and before they finish their migration to the cortex. He based this theory on

several experiments. First, Jensen and Killackey (1984) showed that X irradiation of rat embryos, which inhibits normal neuronal migration, did not prevent the neurons from acquiring their normal morphology and connections. Second, McConnell (1988) showed that transplantation of ventricular layer cells from an embryonic ferret into the telencephalon of a newborn ferret resulted in the transplanted cells' migrating to the cortical layers appropriate for the donor cells. Third, Schwartz and Goldman-Rakic (1986) showed that some neurons actually send off their axons across the corpus callosum while they are still in the process of migrating. Finally, Caviness, Crandall, and Edwards (1988) showed that despite the abnormal migrations of the neurons in mice that are homozygous for the *reeler* mutation, the neurons form the structures and connections appropriate for the time of birth. Therefore, these results strongly suggest that the identity of a neuron is determined before it has migrated to the cortex, and that major changes in its environment do not significantly effect its differentiation.

The adult cerebral cortex can be thought of as an assembly of repeating units made up of ontogenetic columns. Rakic (1988) estimated that the human cortex contains between 150 and 200 million columns, in contrast to the macaque monkey, which contains 10-fold fewer, and the mouse, which has about 100-fold fewer columns. It has been recognized for nearly 35 years that the cerebral cortex is functionally organized in vertical columns (Mountcastle, 1957). For instance, neurons within a single column in the primary sensory cortices respond to the same characteristics, such as receptive field, modality, orientation of light, and ocular dominance (Code & Winer, 1986; Goldman & Nauta, 1977; Hubel, 1988; Jones, Burton, & Porter, 1975). Therefore, the cells within a given ontogenetic column are related to each other developmentally and functionally.

2.3. Functional Specification of the Cerebral Cortical Areas

Superficially, the cerebral cortex appears to be a uniform six-tiered structure made up of ontogenetic columns that are repeated throughout the surface of the telencephalon. If this were true, it would be hard to imagine that the cortex could perform the wide variety of functions it carries out: processing visual and auditory information, regulating movements of the body, forming and retrieving memories, and coordinating all of these activities to produce speech, play a violin, or formulate the theory of relativity. Actually, the cerebral cortex is subdivided into discrete functional domains, many of which have distinctive anatomical differences. These domains are called *architectonic areas* (Mesulam, 1986). In fact, the cortex is made up of several types of structures.

Up to now, we have described the development of the six-layered neocortex. There are other cortical areas with fewer layers. These correspond to the evolutionarily older brain structures of the allocortex (limbic system). Within the allocortex are the hippocampal formation (also known as the *archicortex*) and the primary olfactory cortex (also referred to as the *paleocortex*). These structures contain only two layers of cells. Adjacent to the allocortical regions are the mesocortical (paralimbic) domains, and next to these are the six-layered isocortex (neocortex). There is a gradual transition in the number of cellular layers from the two-tiered allocortex, through the mesocortex (which progressively has three, four, and five layers), to the six-tiered isocortex. Within the neocortex, the varied differences in the histology of the cortex are more subtle, but obvious enough for a 19th-century anatomist named Korbinian Brodmann to distinguish about 50 different cytoarchitectonic areas. Recently, modern techniques have allowed us to discover other unique features of specific cortical domains. For instance, the primary visual cortex has developed a new cellular structure in Layers 2 and 3 called the *blob* (Livingstone & Hubel, 1988). The blob consists of a group of cells with specific functional properties related to color and form vision, which are apparent only when the cortex is stained for a particular enzyme, cytochrome oxidase. Therefore, the cerebral cortex is not a uniform structure. Furthermore, the human brain has evolved lateral specialization. For instance, most spoken-language functions are localized in the left hemisphere. In fact, there is an anatomical correlate to this functional asymmetry: a structure on the upper surface of the temporal lobe, called the *planum temporale*, is longer on the left side of the brain of most individuals (Geschwind & Galaburda, 1985).

At present, there is considerable uncertainty about the mechanism controlling the structural and functional identity of the various cortical regions. There are two prevailing models (Rakic, 1988). The first model proposes that the specification of cortical areas is genetically controlled. The second model suggests that the structure and function of a given cortical area can be molded by the synaptic input it receives from other parts of the brain. In a sense, this is a version of the old nature-nurture debate. Evidence supporting the genetic mechanism is based on many facts; we cite just a few of them here. First, the correct topographic connections are found in the visual cortex in anophthalmic mice (Guillery, Ombrellaro, & LaMantia, 1985). Second, ocular dominance columns develop in the monkey prenatally (Hubel, 1988). These findings show that construction of the highly differentiated visual cortex can occur without visual input. Third, as mentioned earlier in the chapter, the telencephalon is subdivided in several regions during the first weeks of development, so that allocortical, mesocortical, and neocortical regions

begin to develop significantly before synapses have begun to form. This sequence suggests that there is a map of the telencephalic structures, and that the map is genetically encoded. Rakic (1988) hypothesized that two sets of controlling genes would need to exist to encode this system of development. One set would influence the number of ontogenetic columns in a given architectonic domain, and the second set of genes would control the identity of the neuronal phenotypes produced within an ontogenetic column.

The alternative view of specification of the cortical structure and function posits that, initially, all of the cortical neurons are equipotential. The afferent axons (particularly from the thalamus) then instruct the neurons on the type of cortex to form. Some evidence supporting this hypothesis comes from the following elegant experiments. If retinal ganglion cell afferents are rerouted to the auditory thalamus, the thalamic afferents then innervate the auditory cortex (Sur, Garrahy, & Roe, 1988). These investigators found that the primary auditory cortex could now detect visual stimuli, and that many of the electrophysiological properties of the cortex were indistinguishable from the primary visual cortex. Similar experiments were also done by rerouting the visual afferents into the somatosensory thalamus (Frost & Metin, 1985). The results showed that the various primary sensory cortices can function interchangeably. However, it is not known whether more complex aspects of vision, such as stereopsis, color recognition, and movement, can be decoded by the auditory and somatosensory cortices. Furthermore, a more challenging experiment would be to see if a motor cortex or an association cortex could function as a visual cortex.

Another type of experiment that demonstrated that the local milieu has important effects on cortex differentiation involved the transplantation of fetal occipital neurons into the motor cortex of newborn rats. Normally, occipital neurons elaborate axons that transiently enter the pyramidal tracts, but later, these axons degenerate. In contrast, neurons in the motor cortex produce axons that permanently make up the pyramidal tract. Following transplantation of the fetal occipital neurons into the motor cortex, the occipital neurons elaborated axons that became a stable element of the pyramidal tract (Stanfield & O'Leary, 1985). This finding shows that the local environment of the transplanted occipital neurons modified their phenotype. It is not known what aspect of the environment induced the change in the transplanted cells.

Finally, Rakic (1988) performed experiments in which he decreased the number of thalamic afferents to the visual cortex by enucleating embryonic cats. Enucleation leads to significant neuronal cell death in the region of the thalamus involved in vision, which in turn eliminates many of the thalamic neurons that project to the visual cortex. Rakic

found that there was a corresponding decrease in the number of ontogenetic columns that the thalamic afferents innervated. He also determined that the visual cortex appeared normal, based on many cytological and biochemical criteria. He concluded that the cortex can develop independently of input from the thalamus, but that the parcellation of the cytoarchitectonic domains can be affected by thalamic input.

In this section, we have described how the laminar structure of the cerebral cortex is generated. We have also illustrated that the cortex is made up of repeating units of vertical columns of clonally related cells that make up the elementary functional units. At present, although cerebral cortical development is well understood from an anatomical perspective, the underlying molecular mechanisms are not known. We suspect that the early events in cortical development (such as layer formation, and specification of allocortex, (from mesocortex from neocortex)) are controlled by intrinsic characteristics of the developing brain, such as the local chemical environment, cell-cell interactions, and ultimately the genes that are expressed in each cell.

2.4. Development of Other Regions of the Brain

We began our description of brain development by focusing on the cerebral cortex for several reasons. The cerebral cortex, especially the frontal lobes and the regions involved in language production and processing, has specifically increased in size in humans. This increase suggests that the cerebral cortex is required for complex processes such as abstract thought and language. These are cerebral functions that are characteristically disturbed in children affected with disorders of cognitive development. However, there is also evidence suggesting that disorders of subcortical structures, such as the cerebellum and the basal ganglia, may also be involved in human developmental disorders of cognition. Therefore, in this section, we briefly summarize some of the principles of the development of subcortical structures.

Many of the phenomena seen in the development of the cerebral cortex are also found in the development of other parts of the brain. First, most of the structures differentiate from progenitor cells in the ventricular zone. Typically, the ventricular region thickens with the rapidly dividing cells. These thickened regions are the anlage of the subcortical structures. Then, the cells migrate toward the pial surface, a process that we have already described for the cortical cells. However, in the case of subcortical nuclei, such as the thalamus, the basal ganglia, and the brain-stem nuclei, the neurons do not migrate all of the way to the surface; instead, they remain deep in the substance of the brain.

Another difference is that many of these structures do not have

layers of cells like those seen in the cerebral cortex. For instance, the amygdala, the basal ganglia, and most brain-stem nuclei do not have readily apparent layers of cells. On the other hand, other subcortical structures do have orderly layers, such as some of the thalamic nuclei (e.g., the lateral geniculate nucleus, or LGN), the superior colliculus, and the cerebellum. It is interesting that the layering of the LGN is relatively new evolutionarily. For instance, although the primate LGN has six layers (each with specific functions), the rat LGN is not clearly layered. Thus, parts of the brain, such as the LGN, continue to evolve new structures, presumably to increase their ability to perform more complex functions.

Structures such as the caudoputamen complex in the basal ganglia, which do not organize their neurons into layers, display a different type of order. The caudoputamen, whose anlage is first apparent on E35 (Lemire, Loeser, Leech, & Alvord, 1975), is made up of at least two sets of cellular components: the patches and the matrix. Both the patch and the matrix are made up of groups of cells, which differ in their content of neurotransmitters, neurotransmitter receptors, and afferent and efferent connections, as well as in the time in development when each component appears (van der Kooy & Fishell, 1987).

In the developing lateral amygdaloid nucleus, there is an interesting transient structure. Although the adult nucleus appears homogeneous in its distribution of cells, the embryonic nucleus, at 12 weeks of gestation, develops 7-11 columnar cell clusters. These columns then gradually coalesce to form the homogeneous appearance of the adult lateral amygdala (Nikolic & Kostovics, 1986).

Development of the cerebellar cortex exemplifies yet another pattern of morphogenesis (Altman & Bayer, 1985). It has two germinal zones: the ventricular layer and the external granular layer. The cerebellum begins to develop on E28, from the alar plate of the rhombencephalon (Lemire *et al.*, 1975). Rapid cellular division of the progenitor cells in the ventricular layer precedes the neuronal migrations that follow the paths elaborated by the radial glial cells, which are called *Bergmann astrocytes*. These neurons migrate toward the pial surface to form the Purkinje cell layer around E70. This part of cerebellar cortical development is similar to cerebral cortical development. However, a major portion of the cerebellar cortex is also derived from a germinal zone that transiently covers the outer surface of the cortex. Originally, these cells derive from the ventricular zone, but they migrate along the outer surface of the cerebellum to form the external granular layer. It is first apparent on about E60, and mitoses of these cells produce three cell types: the basket and stellate cells (which are interneurons in the cerebellar cortex's most superficial stratum, the molecular layer) and the

granule cells. The granule cells migrate from the cerebellar surface into the substance of the cerebellum, past the Purkinje cell layer, and form the internal granular layer. The external granular layer begins to diminish in size by about E210 but completely disappears only after the two postnatal years. Similarly, the internal granular layer continues to form during postnatal life. This is the only part of the mammalian brain that continues to accrue new cells postnatally.

There is another transient germinal zone in the brain stem, which is called the *corpus ponticobulbare*. This structure forms in the lateral recess of the fourth ventricle. Cells in this mitotically active area migrate to form the olivary, arcuate, and pontine nuclei (Ellenberger, Hanaway, & Netsky, 1969).

Another feature of many regions of the brain, including the cerebral cortex, is that different parts of a given structure develop at different times. Bayer and Altman (1987) reviewed this subject and described the spatial gradients in the birth dates of brain structures. These gradients can have complex patterns; for instance, the caudoputamen complex in the rat has several gradients, including a ventrolateral to dorsomedial gradient in neuronal birth dates (i.e., neurons in the ventrolateral caudoputamen are born before neurons in the dorsomedial caudoputamen).

Therefore, different parts of the brain exhibit different patterns of development, further illustrating the complexity of brain ontogeny. In the next section, we address the issue of how the cerebral cortex is wired to other parts of the brain.

2.5. *Development of Neuronal Connections: Anatomy and Development of the Visual System*

We have chosen to give an overview of the development of the visual system to illustrate several aspects of nervous system development. First, we illustrate how the cerebral cortex is connected to other parts of the brain. Then, we describe the highly intricate process that links neurons from different parts of the brain. We also show that much of the brain is already wired together before a human is born, and we also demonstrate that postnatal experience has profound effects on brain anatomy and function. Although much of what we describe is based on research done on nonhuman primates and cats, there is already substantial evidence that these results apply to humans as well.

There are three major parts in the visual pathway. They are the retina in the eye; the lateral geniculate nucleus in the thalamus; and the visual cortex in the cerebral cortex. The retina consists of three cellular layers. The photoreceptor cell layer (the rods and cones) is linked to the bipolar cell layer, which in turn forms synapses with the ganglion cell layer. The

primordia of the eyes are first apparent on E22 (for details of eye development, see Lemire *et al.*, 1975; Moore, 1977). By E45, the retina is well developed, although not mature, and the ganglion cells are sending their axons out the primitive optic nerve (called the *optic stalk*). By E50, the ganglion cell axons have begun to reach their principle target, the LGN, in the ventral thalamus. The retinal ganglion cells also send afferent axons to the superior colliculus in the midbrain tectum. The axons from the ganglion cells must navigate from the retina, through the optic nerve, and past the optic chiasm and then must choose the appropriate thalamic nucleus to innervate. Furthermore, axons from ganglion cells in the medial half of the retina cross at the optic chiasm, whereas axons from ganglion cells in the lateral half of the retina do not cross at the chiasm. This is an excellent example of the ability of axons to follow precise pathways. We address the topic of axon guidance in greater detail later in the chapter.

The thalamus is a diencephalic structure made up of several collections of cells (called *nuclei*). Many of these nuclei serve as relay stations between the cerebral cortex and more peripheral sensory structures (such as the retina and the cochlea). The thalamic anlage is first apparent as a ventricular swelling on about E33, and the LGN first becomes identifiable on about E45 (Lemire *et al.*, 1975). The human LGN is a six-layered structure (the layers are apparent by about E140), with four dorsal layers containing small cells (the parvocellular layers) and two ventral layers containing large cells (the magnocellular layers) (Livingstone & Hubel, 1988). Each eye projects to both the left and the right LGN. Initially, and each eye diffusely innervates each LGN, but then, later in prenatal development, the synapses undergo a fascinating rearrangement that results in a striking pattern of innervation: each eye innervates three of the six layers of each LGN in an alternating pattern (Rakic, 1977; Shatz, 1983). Therefore, initially, when the retinal axons interact with the LGN, they are distributed throughout the nucleus; subsequently, the axons are redistributed in a precise pattern. Similar phenomena of synaptic redistribution are also seen in many other parts of the developing nervous system, including the cerebral cortex, the autonomic ganglia, the cerebellar Purkinje cells, and the muscle fibers (see Chapter 12 of Purves & Lichtman, 1985, for a discussion of this phenomenon).

The process of synaptic redistribution is complex, but recently, workers have begun to understand some of the mechanisms involved. Several research groups have found that inhibition of synaptic activity prevents the redistribution process. Their experiments have involved pharmacologically inhibiting action potentials in fetal animals, either in the LGN (Sreterevan, Shatz, & Stryker, 1988) or in the retina (Stryker &

Harris, 1986) by using the drug tetrodotoxin. They have found that the redistribution of synapses in the LGN and in Layer 4 of the visual cortex did not occur. These important results show that synaptic activity in the prenatal animal is intimately involved in the development of the brain.

In the next step of the visual pathway, cells in the LGN send axons to the primary visual cortex. Cells from the parvocellular layers of the LGN send axons to Layer 4C alpha, whereas cells in the magnocellular layers send their axons to layer 4C beta (there are also minor projections to Layers 6 and 1) (Livingstone & Hubel, 1988). The axons grow from the LGN toward the cortex and then stop in a region called the *subplate zone*, just below the developing cortex (the cortical plate). In the cat, the axons wait in the subplate for 3 weeks before they reinitiate their trajectory to cortical Layer 4 (Shatz, Chun, & Luskin, 1988). While in the subplate, the axons form synapses with the neurons in the subplate. Later in development, the subplate neurons are no longer apparent, and it is believed that they degenerate. At present, no one knows why the thalamic afferents stop in the subplate zone and form transient synaptic connections with the resident neurons. Shatz (1983) hypothesized that the subplate zone serves an important role in the development of the neocortex and suggested that it may aid in the trajectory of afferent axons toward the cortex, as well as serving as the scaffold for cortical development.

Following the waiting period in the subplate zone, the afferent axons from the LGN grow into the cerebral cortex and innervate cells in Layer 4. During this period, synaptic connections begin to form between the different layers in the cortex. Layers 5 and 6 begin to send axons to subcortical nuclei. Also Layers 2 and 3 begin to send out axons to other cortical areas on the same hemisphere, and across the corpus callosum to the opposite hemisphere. This connection permits different cortical areas to communicate with each other for a wide variety of functions. Layer 4 innervates Layers 2 and 3; Layers 2 and 3 innervate Layers 5 and 6. These connections produce the intrinsic wiring required for cortical functioning. Furthermore, axons from several brain-stem nuclei (including the locus coeruleus and the raphe nuclei) arrive and innervate all of the layers of the cortex. The process of maturation of the cortex takes many months and involves growth of the neurons, the elaboration of dendrites, the formation and rearrangement of synapses, and finally the myelination of the axons.

Among the many fascinating things that occur during this process is the formation of the ocular dominance and orientation columns. Initially, neurons in Layer 4 can be stimulated by both the left and the right eye. However, during development, there is a rearrangement of synaptic input that results in the formation of alternating columns of neurons,

each of which is predominantly stimulated by only one eye (see Hubel, 1988, for a description of this phenomenon). This process is reminiscent of the synaptic rearrangement that also occurs in the LGN. This subject is expanded on later in this chapter, when we discuss the effects of visual deprivation on cortical function and anatomy. There is also the development of orientation columns in the primary visual cortex. These are vertical columns of cells spanning the cortex that are stimulated when a bar of light oriented at a specific angle is seen by the eye (Hubel, 1988).

The primary visual cortex is linked to several visual association cortices (e.g., visual area 2, V4, and MT) via axons emanating from Layers 2 and 3 (Livingston & Hubel, 1988). The association cortices further process the visual information. They segregate visual information into its elementary parts: color, form, depth, and movement. The visual association cortices are then linked to other parts of the brain involved in complex tasks such as the formation of memory, the decoding of visual information into language (reading), and responses to visual information with affect and motonic behavior (i.e., fearfully running from a lion).

This discussion illustrates that different regions of the cerebral cortex are parcelled out to perform specific functions, and that specific axonal connections link these independent functional domains together. In the next section, we discuss current ideas regarding how axons follow specific paths, and how they choose the appropriate cells to form a synapse.

2.6. Axon Pathway Guidance and Synaptic Specification

In order for the nervous system to have its precise organization, axons must follow specific routes to reach their appropriate target cells, whether they be a neuron, a muscle, or a hormone-producing cell. Furthermore, in the brain, axons must choose among vast numbers of target cells to form the correct synapse. At present, we do not know how this process is accomplished; however, there is mounting evidence that it occurs, at least in part, through a system of cell adhesion molecules.

This subject has been extensively studied in lower vertebrates by examining the axonal projections from the retinal ganglion cells to a midbrain structure called the *optic tectum*. In amphibians, the optic tectum, which corresponds to the superior colliculus in mammals, is the principle brain structure involved in visual perception. The axons from the retinal ganglion cells follow the optic nerve, cross at the optic chiasm, and then follow the optic tract to the tectum, where they innervate cells in a precise pattern, reproducing the retinal map on the tec-

tum. Hence, the geometric cellular relationships of retinal ganglion cells are maintained in the optic tectum. This process illustrates that there is a highly ordered mechanism for specifying synaptogenesis.

The classic experiments of Sperry in the 1940s (see Purves & Lichtman, 1985, for a review) led the way to an understanding of this process. In these experiments, Sperry cut a frog's optic nerve, rotated the eye 180 degrees, and allowed the retinotectal axons to regenerate and to reinnervate the tectum. The animal was able to recover vision in the operated eye, but the visual field was now inverted 180 degrees; objects below the frog appeared above it. This finding suggested that the retinotectal axons had reinnervated the tectum in the same pattern as they had had before the eye was rotated. The retinal ganglion cells in the ventral part of the retina now innervated the dorsal region of the tectum, instead of the ventral tectum. Therefore, retinal axons from each part of the retina have a specific affinity for particular parts of the tectum. This finding led Sperry to propose the chemoaffinity hypothesis, which postulates that cells and axons have "individual identification tags" that specify which cell will form a synapse with a particular axon. A corollary is that axons must also use similar processes for determining which path to follow. For instance, in the mammalian optic chiasm, axons from the nasal half of the retina cross at the chiasm, whereas axons from the temporal half of the retina do not cross. This is just one example that clearly illustrates that axons follow very specific paths.

Sperry's results have stimulated many workers to identify the molecules involved in these processes. A variety of *in vitro* systems have been developed, using either chicken (Walter, Henke-Fahle, & Bonhoeffer, 1987) or goldfish (Vielmetter & Stuermer, 1989) tectal membranes as targets for retinal axons. The researchers have found that axons from some regions of the retina preferentially grow onto particular regions of the tectal explants; however, axons from other regions of the retina grow on the entire tectal explant. At present, the molecular details of this process are not known, but Walter, Henke-Fahle, & Bonhoeffer (1987) proposed the novel idea that there may be substances on the tectal surface that repel some classes of neurons. This is an excellent model system for aiding in the identification of the molecules that determine how axons choose particular cells as their targets for synapse formation.

Other researchers have focused directly on the process of how axons choose the pathway that they are going to take. These results have shown that there is little question that there are molecular signposts that direct the axon's route. For instance, Harris (1989) rotated the neuroepithelium in the region of the presumptive optic tract in a *Xenopus* (toad) embryo 90 degrees clockwise. He performed this manipulation before the retinal axons had grown into the optic tract. He discovered that, when the axons did arrive in this region, they turned 90

degrees clockwise, presumably following the cues provided by the rotated neuroepithelium.

At present, a number of molecules are implicated either as providing the signposts to the axons or as being the identification tags on axons and neuronal cell bodies. This subject has been recently reviewed by Harrelson and Goodman (1988) and by Dodd and Jessell (1988). These molecules can be subdivided into four classes: (1) extracellular matrix proteins that serve as surface to stimulate (or inhibit) the growth of axons; (2) cell-surface proteins that bind to extracellular matrix proteins; (3) cell-surface proteins that promote nonspecific cell-cell adhesion; and (4) cell-surface proteins that are found only on axons, and that promote specific axon-axon, axon-dendrite, and axon-cell-body adhesion.

A number of extracellular proteins are implicated in the promotion of axonal growth. These include fibronectin, tenascin, thrombospondin, collagen, and laminin (Dodd & Jessell, 1988). These proteins are found in a structure called the *extracellular matrix*, which, among its many functions, can serve as surface on which axons can grow. Laminin is particularly interesting for two reasons. First, it is found in only limited regions of the developing nervous system and therefore could play a role in promoting specific axonal growth. Second, axons interact with laminin via a family of cell-surface receptors called *integrins* (Buck & Horwitz, 1987). The integrins are made of two subunits, alpha and beta; different combinations of the subunits create the family of receptor molecules, each of which has different affinities for laminin and other extracellular matrix elements.

There is also a class of cell-surface glycoproteins that promote cell-cell adhesion via homophilic interactions. These proteins are found ubiquitously in the nervous system and are expressed both on the cell body and on axons. An example of a homophilic interaction is as follows: A cell expressing glycoprotein A, via an interaction between the two glycoprotein A molecules. Two molecules, neural cell adhesion molecule (N-CAM) (Edelman, 1988) and N-cadherin (Takeichi, 1988) are examples of this type of cell-surface glycoprotein; they are found ubiquitously on both developing and differentiated neurons.

Finally, there is a class of axonal glycoproteins whose expression is limited to the axonal surface. These include L1, G4, F11, neurofascin, TAG-1, contactin, and TRAP in vertebrates (Dodd & Jessell, 1988), and fasciclin I and II and amalgam in insects (Harrelson & Goodman, 1988). Some of these glycoproteins (fasciclin II, F11, TAG-1 and TRAP) are found on only a small subset of axons at a given time in development. Therefore, these proteins are likely candidates for the molecular tags that help determine axon pathway choice and eventually synaptic choice. Another intriguing aspect of these proteins is that some of their amino acid sequence shows similarity to the amino acid sequence of the constant

region of immunoglobulin molecules (Brummendorf, Wolff, Frank, & Rathjen, 1989; Harrelson & Goodman, 1988). This finding suggests that the nervous system and the immune system may use similar recognition mechanisms.

No discussion of axon pathway guidance is complete without a description of the growth and tropic factors that are found in the nervous system. The best known and studied is the nerve growth factor (NGF) discovered in the 1950s by Levi-Montalcini, Cohen, and co-workers (for a review of this subject, see Barde, 1989; Purves & Lichtman, 1985). NGF appears to be required for the survival of sympathetic-chain and dorsal-root-ganglion neurons. There is also evidence that NGF serves an important role in the physiology of cholinergic neurons in the forebrain. Another important growth and tropic factor is called the *brain-derived neurotrophic factor* (BDNF) (Barde, 1989). BDNF, in conjunction with the extracellular matrix protein laminin, supports the survival of dorsal root ganglion cells in culture. A third growth and tropic factor is fibroblast growth factor (FGF) (Barde, 1989).

NGF, BDNF, and FGF all have several properties in common. They are small proteins that are present in small quantities in the nervous system, as well as in other tissues in the case of NGF and FGF. They are tropic substances, in that axons will grow toward a source producing these molecules. Furthermore, they are growth factors. Certain sets of neurons will die if their supply of these proteins is cut off. If the concentration of these proteins is increased, they prevent the programmed cell death that occurs in most parts of the developing nervous system. Currently, it is believed that these growth and tropic factors serve several functions. They are probably required to maintain the survival of axons that have formed a stable synapse with the appropriate target cell. Second, they may be important in stimulating the growth of axons and possibly of cells during development. Third, they may aid in axon pathway guidance. Fourth, they may play a role in neuronal differentiation. Finally, they may be involved in supporting the growth of axons during regeneration.

We have summarized several of the known mechanisms that axons use to specifically traverse the nervous system en route to their targets. It is probable that no one mechanism is used to achieve this complex process, and that a combination of some or all of the described phenomena is required for an axon to reach its destination efficiently and accurately.

2.7. Maturation of Synapses

Once an axon has reached its destination, it must form a functional synapse with its target cell. Many separate steps are involved in making

a synapse, and we will only superficially cover some of the major points. The process can be divided into several parts. First, the axon must be able to propagate an electrical impulse, called the *action potential*. To do this, the axon must contain membrane proteins that can function as voltage-gated ion channels and as ion pumps (see Kuffler, Nicholls, & Martin, 1984, for a review of this subject). Next, the axon terminus must develop the ability to synthesize and release neurotransmitters. There are a wide variety of neurotransmitters, which can be subdivided into two general categories: peptide and nonpeptide. Examples of nonpeptides include catecholamines (norepinephrine and dopamine), serotonin, histamine, adenine, gamma amino butyric acid (GABA), and glutamine. Examples of peptide neurotransmitters are enkephalin, endorphin, cholecystokinin, and substance P. Different types of neurons produce different neurotransmitters. For instance, cells in the brain-stem nucleus called the *locus coeruleus* synthesize norepinephrine, whereas cells in the raphe nuclei synthesize serotonin. Neurotransmitters are stored inside vesicles; the vesicles release the transmitters when an action potential stimulates an influx of calcium into the axon terminus.

Neurotransmitters are released into the space between the axon terminus and the target cell. The target cell produces small antenna-like structures called *dendrites*, which are the true targets of the axons. The dendrites have specialized appendages, called *spines*, that form the synapse with the axon. The spines contain membrane proteins that bind to neurotransmitters; these proteins are called *neurotransmitter receptors*. When the receptor binds the neurotransmitter, it initiates either a chemical or an electrical signal in the target cell. The signal can do a variety of things, including initiating an action potential in the target cell, inducing chemical changes in specific proteins via phosphorylation, and changing the level of expression of specific genes.

The development of these various anatomical, electrophysiological, and biochemical processes follows a strict sequential pattern (see Parnavelas *et al.*, 1988, for a review of the development of neurotransmitters, and Armstrong-James & Fox, 1988, for a review of the development of neuronal physiology in the cerebral cortex). Although many of these processes take place prenatally (especially the formation of the rudimentary components of synaptic function), the production of stable synapses, especially in the cerebral and cerebellar cortex, occurs postnatally. Therefore, the pattern of cortical synapses depends in part on the environmental stimuli that the animal experiences. We will elaborate on this topic in more detail in the section on critical periods in development.

A fundamental process seen in neurodevelopment is that axons in many parts of the nervous system initially make an overabundance of synapses. For instance, thalamic afferents carrying information from

both eyes form synapses diffusely in Layer 4 of the primary visual cortex. Then, later in development, during the process of synaptic rearrangement, the ocular dominance columns form. This process involves the stabilization of some synapses and the removal of others. Several laboratories have discovered anatomical correlates of this process. For instance, Michel and Garey (1984) found that the number of dendritic spines (which are believed to correlate directly with synapse number) and the number of synapses change significantly during development. They specifically studied Layer 3 of the human primary visual cortex and showed that there are twice as many spines and synapses on neonatal human dendrites than on dendrites of a 33-week-old fetus. The number of spines reaches a maximum at 5 postnatal months (three-fold greater than the 33-week fetus), and then, the number decreases to adult levels (two-fold more than the 33-week fetus) at around 2 years of age. These results show that the anatomy of the human visual cortex continues to change postnatally. They also show that the adult visual cortex has fewer synapses than that of the 5-month-old baby. This finding points out that more synaptic connections do not necessarily correlate with higher levels of brain function. The nature of the synapses is just as important as their absolute numbers.

Another fundamental process in neurodevelopment is the death of neurons. Evidence suggests that many neurons that fail to form stable synapses with their targets either die or atrophy. Although most of the evidence that supports this possibility has come from work done on the spinal cord, it is likely that similar events also take place in the brain. The mechanism(s) underlying this phenomena is not fully understood but may involve competition for growth factors produced by the target cells; only those axons that successfully compete to form a synapse with the appropriate target cell can take up the growth factor they need to survive (Purves & Lichtman, 1985).

2.8. Myelination

Myelination is a process in which a glial cell (called an *oligodendrocyte* in the central nervous system and a *Schwann cell* in the peripheral nervous system) wraps itself around an axon, to form a multilayered fatty sheath. This sheath insulates the axon and significantly increases the velocity at which the action potential propagates along the axon. Inadequate myelination results in neurological impairment. Axons in different regions of the nervous system are myelinated at different times in development. For instance, myelination of in the spinal cord begins around E84, whereas in the association areas of the cerebrum, it does not actively begin until the first months after birth (Lemire *et al.*, 1975).

Several rules determine when axons in specific parts of the nervous system become myelinated (Kinney, Brody, Kloman, & Gilles, 1988): Proximal pathways myelinate earlier and faster than distal pathways; sensory pathways myelinate before motor pathways; projection pathways myelinate before association pathways; and in the telencephalon, myelination progresses from central sites to the poles (the occipital pole myelinates before the frontal pole, and the temporal pole myelinates last). This sequence shows that the pathways involved in higher cognitive function (such as associative pathways) are among the last to be myelinated.

2.9. Critical Periods in Development

Development of the brain involves a carefully orchestrated set of processes that require a precise set of spatial and temporal regulatory mechanisms. The neural tube is divided into discrete anatomical domains that differentiate into specific parts of the brain. Similarly, the timing at which the various processes occurs is extremely important. This fact is best illustrated by the concept of *critical periods of development*. A critical period represents the window in time during which a developmental process must take place. If completion of the process is inhibited, that developmental step will never be achieved, and sequential processes dependent on it will similarly be arrested.

Critical periods have been identified in the development of many parts of the brain. For instance, in rats, the axons of the corticospinal tract descend through the spinal cord during the first postnatal week. If the spinal cord is damaged during the first 5 days of life, before the axons arrive, the axons are able to reroute around the damaged tissue. However, if the spinal cord is damaged after Postnatal Day 5, the axons lose their ability to form an alternate pathway around the lesion (Bregman, Kunkel-Bagden, McAtee, & O'Neill, 1989). Bregman and coworkers suggested that after Postnatal Day 5, the factors necessary to allow the axonal rerouting are no longer produced. Hence, the plasticity of the nervous system has strict temporal constraints; similarly, repair to damaged parts of the brain can occur only early during development.

Development of vision also has well-described critical periods. It has long been known that, if cataracts are not removed before the age of 8, a child will remain blind for life. Similarly, if a child has strabismus in one eye, vision in that eye will remain impaired if it is not properly aligned at an early age. Landmark experiments by Hubel and Wiesel using cats and monkeys have elucidated many of the mechanisms underlying critical periods in the development of cerebral cortical function (see Hubel, 1988, for a review of their work). They found that, if a

monkey's or a kitten's eyes were sutured closed during the first several weeks of life, its vision was permanently damaged. They discovered that the retina remained entirely functional, but that the LGN and the visual cortex had specific abnormalities. The cells in the layers of the LGN supplied by the nonfunctional eye had decreased in size, although functionally they behaved normally. The primary visual cortex had both striking functional and anatomical abnormalities. As we have already described, Layer 4 in the normal primary visual cortex has alternating columns of cells that respond predominantly to stimulation from one eye. In the animals who had vision impaired in one eye during the critical period, the cells in Layer 4 responded only to stimuli from the normal eye. Furthermore, cells in Layer 4 formed synapses only with LGN cells that relayed information from the normal eye. Closure of an eye outside the critical period did not result in these abnormalities.

Hubel and Wiesel (Hubel, 1988) then discovered a mechanism that explained their findings. Normally, during development, there is a uniform binocular projection of LGN axons to Layer 4. Therefore, initially, there are no ocular dominance columns in the cortex. Then, through the process of synaptic rearrangement, the ocular dominance columns develop. However, if one eye does not provide stimulation to the cortex during the postnatal critical period, the synapses between its LGN axons and the Layer 4 cells are lost. Conversely, synapses stimulated by the normal eye are strengthened. These researchers concluded that there is a competition between the LGN axons for the Layer 4 cells, and that at least part of the competition is strongly modulated by synaptic activity (i.e., visual experience).

Several other laboratories have replicated these results as well as identified other critical periods and determined the effects of specific types of sensory deprivation on the structure and function of the cerebral cortex (see Hubel, 1988). All of these results strongly suggest that development of the brain follows specific blueprints that set up an initial wiring diagram. The wiring diagram can, however, be modified by deprivation of visual experience. This powerful result shows that normal brain function requires both proper biological development and correct environmental stimuli. Nature and nurture are both important.

The issue of critical periods in the development of human cognitive, social, and emotional functioning remains open. Evidence from experiments involving emotional and social deprivation in monkeys (Harlow & Harlow, 1973) strongly suggests that critical periods do exist for these facets of brain function. Obviously, well-controlled experiments involving these types of deprivation cannot be done in humans, but it is clear to us, as well as to many mental health professionals, that emotional trauma in childhood can leave irreversible scars. However, it is pre-

mature to say whether the etiology of a particular form of mental illness is due to abnormal nature or abnormal nurture.

3. *Mammalian Developmental Neuropathology*

We have reviewed the major steps in the construction of the human brain. Each step is extremely complicated, itself consisting of a variety of biochemical and biophysical processes. Governing the assembly of the brain are genes, which encode the proteins that serve as the enzymes, the transcription regulator molecules, the cell adhesion molecules, the ion channels and pumps, the neurotransmitters, the neurotransmitter receptors, the growth and tropic factors, and the cytoskeletal subunits. It has been estimated that there are 100,000 different messenger RNAs that are used only to make the nervous system (Hahn, Chaudari, Sikela, & Owens, 1986). Thus, there are an immense number of genes that must function properly in order to construct a normal brain. There is an equally large number of possible mutations that can lead to abnormal brain development. In this section we review the major types of neuropathology seen in the developing human brain, as well as a few selected neurogenetic diseases in the mouse. The etiologies of the abnormalities are varied, but they fall into two general classes: genetic and nongenetic. The genetic abnormalities include point mutations, deletions, rearrangements, and duplications in the genes whose products are required for normal brain development. The nongenetic etiologies range from radiation, toxins (such as ethanol and lead), infections (such as rubella, cytomegalovirus, toxoplasmosis, and herpes), cardiopulmonary insufficiency, malnutrition, hormonal deficiency (such as of thyroid and growth hormone), and tumors.

3.1. *Disorders of Neural Tube Formation*

The formation of the neural tube involves the folding of the neural plate into a cylindrical structure between E20 and E30. Failure of fusion of the neural fold results in neural tube defects, also known as *dysraphia* (Lemire *et al.*, 1975). Any part of the neural tube may be affected; the nature of the defect depends on where the neural tube fails to fuse. For instance, if the neural tube does not close in its anterior region, the brain and skull will not form in the region of the defect; this is called *craniorachischisis*, if the entire brain and skull are effected, and *anencephaly*, if only part of the brain and skull is effected. These lesions, which are not compatible with life, are relatively common; as many as 1 in 1000 births is affected. If the defect occurs in the spinal cord, it is called a *men-*

ingomyelocle. These lesions are usually compatible with life but produce severe disabilities in the affected children. The etiologies of neural tube defects are not known for certain, but there are clear genetic components. Furthermore, there is a recessive mutation in the mouse, called *vacuolated lens (vl)*, which causes caudal neural dysraphism (Wilson & Wyatt, 1986).

3.2. Focal Agenesis and Hypoplasia of the Brain

Occasionally, part of the nervous system does not form, or if it does, it is significantly smaller than normal. The most striking example of agenesis is holoprosencephaly, a disorder in which the primary defect is failure of the paired telencephalic vesicles to evaginate (Lemire *et al.*, 1975). In the extreme form, the result is a telencephalon with a single ventricular cavity. Holoprosencephalies comprise a variety of related anatomical abnormalities in which the midline cleavage of the prosencephalon does not occur, and the result is abnormal development of parts of the telencephalon. The olfactory bulbs and tracts do not form, even in the mildest cases. Many of these cases are caused by chromosomal abnormalities, such as trisomy 13.

Agenesis of the cerebellum also occurs associated with agenesis of the cerebellum. There is also a report of two cases of agenesis of the cerebellar vermis, with fusion of the dentate nuclei and the cerebellar hemispheres (Issac & Best, 1987). The symptoms of patients with agenesis of the vermis vary from having virtually no neurological signs with normal intelligence, to ataxia and mental retardation. At present, it is unclear why there is such variability in the symptoms, but this variability may relate to pathology in other parts of the brain, occurring in conjunction with the cerebellar abnormalities.

Hypoplasia of the cerebellum results from a wide variety of etiologies (Sarnat & Alcala, 1980). It rarely occurs in humans as a result of an autosomal recessive mutation. It is also found in a variety of degenerative diseases, such as Werdnig-Hoffmann, Tay-Sachs, and Menkes disease. It occurs in association with developmental anomalies such as the Arnold-Chiari and the Dandy-Walker malformations. In experimental animals, hydrocephalus leads to hypoplasia specifically of the cerebellar vermis. On the other hand, vermal hypoplasia is also found in people who do not have hydrocephalus. Experimentally, cerebellar hypoplasia can be induced with cytotoxic drugs (cyclophosphamide, 5-fluoro-2'-deoxyuridine, cytosine arabinoside, tricyclic antidepressants, and methyloxymethanol), irradiation, and viral infections (feline panleukemia virus, BVD-MD virus, lymphocytic choriomeningitis virus, and parvoviruses).

Recently, several groups (Courchesne, Yeung-Courchesne, Press, Hesselink, & Jernigan, 1988; Gaffney, Tsai, Kuperman, & Minchin, 1987; Murakami, Courchesne, Press, Yeung-Courchesne, & Hesselink, 1989) have found that some patients with the autistic syndrome have hypoplasia of vermal lobules VI and VII, as well as reduced cerebellar hemispheric size. Neuropathological examination has confirmed that there are reduced numbers of Purkinje cells (Bauman & Kemper, 1985; Ritvo, Freeman, Schiebel, Duong, Robinson, Guthrie, & Ritvo, 1986). Bauman and Kemper also found other abnormalities, including decreased numbers of cerebellar granule cells and increased cell-packing densities in the hippocampus, the entorhinal cortex, the septal nuclei, the mammillary body, and selected nuclei of the amygdala.

Cerebellar pathology has also been found in patients with schizophrenia (Snider, 1982). Computerized tomography has shown that about 10% of schizophrenics have atrophy of the dorsal vermis (Heath, Franklin, & Shraberg, 1979), and an autopsy study found anterior vermian atrophy in 3 of 12 patients (Weinberger, Kleinman, Luchins, Bigelow, & Wyatt, 1980).

3.3. Disorders of Neuronal Migration

This subject, which has recently been reviewed (Barth, 1987), deals with disorders in the migration of newly born neurons from the ventricular layer to their specified location. Barth provided a long list of the genetic and environmental causes of these disorders, and we will examine a few of the examples. The disorders are classified according to their morphology, which unfortunately tells us very little about their mechanisms. There are eight major classes: agyria, microgyria, verrucose dysplasia, leptomeningial heterotopia, intra-axial neuronal heterotopia, schizencephaly, cerebellar cortical dysplasias, and olivary heterotopia.

Agyria, also known as lissencephaly, denotes a smooth brain without secondary sulci. This disorder leads to profound neurocognitive retardation. One form of agyria, which is associated with microcephaly, has an abnormally thickened neocortex consisting of four layers. Layer 1 corresponds to the molecular layer; Layer 2 has neurons that have morphologies similar to neurons normally found in Layers 3, 5, and 6; Layer 3 has very few cells; and Layer 4 contains islands of neurons called *heterotopias*. This agyria can be caused by a genetic disorder called *Miller-Dieker syndrome*, in which there is, in some cases, a deletion in chromosome 17.

A second form of agyria is characterized by almost total disorder of cortical layer formation. Normally, the mature cerebral cortex has horizontal layers of cells. In this disorder, the cortex has clusters and vertical

columns of neurons. There are at least two autosomal recessive disorders that produce this pattern of neuropathology, the HARD + / - syndrome (hydrocephalus, agyria, retinal dysplasia, with or without encephalocele) and Fukuyama's congenital cerebromuscular dystrophy.

Microgyria describes a disorder in which the brain has small meaning gyri without intervening sulci, which are commonly associated with abnormalities of cortical layering (either with total disorder or with four layers). There have been two reports of human fetuses that were exposed to carbon monoxide between Weeks 20 and 24 of gestation; the result was the four-layer form of this pathological phenotype. Another case, which resulted from presumed fetofetal transfusion at 13–16 weeks of gestation in parabolic twins, cause microgyria with an unlayered cortex. Microgyria is also associated with two inherited metabolic disorders related to peroxisomal dysfunction: Zellweger cerebrohepatorenal syndrome and neonatal adrenoleukodystrophy. Although extensive microgyria is associated with severe neurological impairment, microgyria that is localized to only part of the brain leads to specific impairments. For instance, Galaburda and Kemper (1979) found that a man with developmental dyslexia had microgyria localized to regions of his brain involved in language function. Another report found similar dysplasias in a girl who had developmental dysphasia (Cohen, Campbell, & Yaghai, 1989).

The third class of neuronal migration disorders leads to verrucose dysplasia, or brain warts. These are tiny herniations of the second neocortical layer (sometimes, of all of the layers) into the first layer. Mild forms of this abnormality can be found in 16%–26% of brains. This disorder is common in children who have neonatal glutaric aciduria Type II.

The fourth class is leptomeningeal heterotopias, which are collections of astrocytes with or without neurons in the first cortical layer.

The fifth class is nodular neuronal heterotopias in the cerebral hemispheres. These represent the clearest example of abnormal neuronal migration. Most commonly, these islands of neurons are found just below the neocortex. The causes of the heterotopias span the genetic and nongenetic categories.

The sixth class is schizencephaly, which describes a cleft in the brain surface, which is commonly associated with a microgyric four-layered cortex and heterotopias.

The seventh class are cerebellar cortical dysplasias and heterotopias. The usual heterotopia is a patch containing a disordered array of granule cells, molecular layer, and Purkinje cells. These may be seen in routine autopsies of "normal" infants and are also common in a variety of disorders such as the Dandy-Walker syndrome, and in GM2-gangliosidosis.

The final class of neuronal migration disorders is heterotopia in the brain stem involving olivary components.

There are several mutations in the mouse that also affect neuronal migration. Two recessive mutations, *reeler* and *weaver*, are particularly interesting. In mice homozygous for the *reeler* gene, the pattern of neocortical layering is inverted (Caviness *et al.*, 1988). Careful study of this mutant mouse suggests that the primary defect is in the process of neuronal migration. Despite the inversion of the cortical layers, the wiring of the cortex appears to be normal.

Both *weaver* and *reeler* mutants have abnormalities in the cerebellar cortex. In *reeler* mice, the Purkinje cell layer is not arranged as an orderly plate; instead, the Purkinje cells are scattered in the periphery of the cerebellar cortex (Goffinet, 1983). In *weaver* mice, the cerebellar phenotype is characterized by a decreased number of internal granule cells. The primary defect probably lies in the ability of the granule cells to migrate from the external granular layer to the internal granular layer (Caviness & Rakic, 1978; Smeyne & Goldowitz, 1989). An elucidation of the gene products that are affected in these mutant mice will greatly aid in the understanding of the molecular events required in orchestrating the complex process of neuronal migration.

3.4. Disorders of Pathway Formation

There are a variety of disorders in humans in which major pathways of axons are either absent or abnormal in their structure. The most striking of these is agenesis of the corpus callosum, a condition caused by a variety of genetic (i.e., Aicardi syndrome) and nongenetic (fetal alcohol syndrome) etiologies (Jeret, Serur, Wisniewski, & Lubin, 1987). There are a large number of reports of abnormalities of the corticospinal tract, ranging from congenital absence (Chow, Halliday, Anderson, Danks, & Fortune, 1985) to anomalous crossing (Roessmann & Hori, 1985). Pathologists have also reported abnormal pathways of spinal posterior roots and spinal sensory tracts (Hori, 1988). A particularly intriguing observation is that, in albino mammals (which have a genetic defect in the production of melanin), the optic tracts do not cross properly at the optic chiasm (Guillery, 1974). In our opinion, these various disorders represent just the tip of the iceberg, and with more refined anatomical methods, many more defects affecting the formation of specific pathways will be discovered.

3.5. Disorders of Myelination

Myelination is vulnerable to a wide variety of insults, including hormone deficiency (Noguchi, 1988); chemical toxins, such as ethanol

(Jones, 1988), methylmercury, lead, tin, and hexachlorophene (Wiggins, 1986); genetic metabolic diseases, such as urea cycle defects and phenylketonuria; and autoimmune inflammatory diseases. There are a number of mouse mutants with neurological symptoms whose primary defect is in the formation of myelin. These include *jumpy*, *shiverer*, and *trembler* (Henry & Sidman, 1988). Recently, the molecular basis for the *shiverer* mutation was found to be a deletion in a major protein in myelin, the myelin basic protein (Popko, Puckett, Lai, Shine, Readhead, Takahashi, Hunt, Sidman, & Hood, 1987).

3.6. Disorders of Synapse Formation

The whole array of nongenetic etiologies that affect brain development also have effects on synapse formation. There are also a variety of inherited illnesses associated with mental retardation that also exhibit pathological changes of the dendrites and, therefore, of the synapse. Purpura (1975) proposed that abnormalities of the dendritic spine are an important factor in many cases of developmental cognitive impairment. He has focused his studies on the AB variant of Tay-Sachs disease, a ganglioside storage disease, and has found a swelling at the base of the axon called a *meganeurite*. The meganeurite elaborates dendrites and dendritic spines, which continue to maintain their structure while the normal apical dendrites degenerate.

Patients with Down syndrome also exhibit abnormalities in their synapses. In this disorder, there is marked progressive dendritic atrophy in the cerebral cortex with aging (Takashima, Ieshima, Nakamura, & Becker, 1989). Patients with Bourneville's disease (tuberous sclerosis) have also been shown to have a variety of abnormalities in the structure of cerebral cortical dendrites (Machado-Salas, 1984).

A mouse neurological mutant called *staggerer* exhibits an abnormality in the dendritic morphology of the cerebellar Purkinje cell. The Purkinje cell dendrites lack spines. In this case, the molecular basis for the mutation lies in the absence of a 400-kilodalton glycoposphoprotein called P400 (Maeda, Niobe, Inoue, & Mikoshiba, 1989). At present, the function of P400 is not known.

3.7. Degenerative Disorders

A large number of neuropsychiatric disorders of childhood manifest themselves postnatally and result from degeneration of the nervous system, rather than a specific disruption in the assembly of the brain. Therefore, these are not truly developmental neurological illnesses, except for the fact that they occur in a brain that is still myelinating its axons and maturing at the synaptic level. A variety of genetic metabolic

illness, such as the lipid storage diseases, phenylketonuria, urea cycle defects, and purine metabolic defects, manifest largely themselves in infancy. Rett syndrome is an example of another neurodegenerative disorder in which there is diffuse cerebral cortical atrophy, underpigmentation of the substantia nigra, abnormal neurites in the frontal cortex and the caudate nucleus, and pathology in the peripheral nerves and muscle (Jellinger, Armstrong, Zoghbi, & Percy, 1988). This disease, which affects only girls, is also interesting because autistic behavior frequently antedates the progressive dementia, ataxia, and loss of purposeful hand use seen in these patients (Hagberg, Aicardi, Dias, & Ramos, 1983).

4. Conclusion to Sections 2 and 3

In Section 2 of this chapter, we summarized the major steps involved in human brain development. The steps include formation of the neuroepithelium, folding of the neuroepithelium into the neural tube, subdivision of the neural tube into functionally distinct domains, migration of the primitive neurons and glia from the ventricular zone to their appropriate location, differentiation of the neurons and glia, elaboration of axons that course their way to specific destinations, development of dendrites, formation of synapses, synaptic rearrangement to remove unsuitable synapses and to strengthen appropriate synapses, death of neurons that do not engage in useful synapses, and myelination of axons. These processes occur in a strict temporal order, which is defined by critical periods during which the process must occur to ensure an optimal result. We have summarized the major steps in the development of the human brain in Table 1.

In Section 3, we reviewed examples of disorders in humans and mice in which these steps of normal development have failed. In most of the cases, the molecular basis for the neuropathological disorder is not known. The studies of the mouse mutants hold the greatest promise in the near future for understanding the molecular basis of abnormalities in neurodevelopment. However, the tools of molecular biology will facilitate research into the biochemistry of the human disorders as well.

In the next section, we discuss the known causes of pervasive developmental disorders (e.g., autism) in humans. We believe that an understanding of normal brain development will help elucidate the neuropathological mechanisms of these diseases.

5. Biological Basis of Autism

In this section, we examine the biological basis for a specific developmental neuropsychiatric disorder: autism. We describe the range of

neuropsychological findings in autistic people as well as review some of the causes of this disorder.

Autism has baffled and intrigued professionals since it was first described (Kanner, 1943). It is a disease that attacks the core of what it means to be human, that is, interpersonal socialization and complex language. Historically, autism had been considered a failure of the development of normal bonding between infant and mother; although this conception recognized the developmental nature of autism, it laid unnecessary blame on the parents of the affected child. Since the early 1970s, it has been appreciated that autism is a biological disorder of the brain.

Children with autism demonstrate severe impairments in the triad of social relatedness, play, and communication. They also demonstrate a variety of other behaviors and cognitive deficits, including stereotypical movements, rigid adherence to routines, impaired imagination, and bizarre use of objects. These children are frequently described by their parents as "children who are in their own world" and "children who tune out." Their language ranges from mutism to full sentences with oddities such as echolalia, pronominal reversals, and idiosyncratic statements. Most children with autism are mentally applying their knowledge to everyday living situations. The incidence of autism is approximately 1 per 10,000 children, with a 4:1 male predominance.

Autism varies widely in its clinical presentation. For example, one individual may be mentally retarded, mute, and socially isolated and may exhibit hand flapping, whereas a second is of normal intelligence but exhibits perseverative behavior and is unable to engage in reciprocal conversation. Furthermore, as this review describes, autism is caused by a range of different illnesses, such as prenatal infection with rubella, fragile X, and phenylketonuria (PKU). Thus, autism is not a disease entity, a syndrome caused by multiple etiologies.

We have subdivided this section into two parts. In the first, we review the major research avenues that are now being pursued to understand autism. In the second part, we review some of the known etiologies of autism. In this chapter, we summarize only the principal information, some of which has been reviewed earlier (Ciaranello, VandenBerg, & Anders, 1982); the reader is referred to the list of references for more detailed reviews.

5.1. Neurobiological Research

Neurobiological research on autism has focused on five methodologies: genetic, neuropathological, radiological, neurophysiological,

and neurochemical. Each of these have uncovered pathological findings in subsets of autistic patients.

5.1.1. Genetics

Genetic studies have included epidemiological and karyotypical analyses. Twin studies have shown an increased concordance for autism among monozygotic as compared to dizygotic twins. The concordance rate of autism for monozygotic twins ranges between 36% and 100%, and the concordance rate for dizygotic twins ranges between 0% and 36% (Folstein & Rutter, 1988; Rimland, 1964; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985; Smalley, Asarnow, & Spence, 1988). Family studies have revealed a 1.3%–2.8% concordance rate among siblings of children with autism (August, Steward, & Tsai, 1981; Campbell, Rosenbloom, Perry, George, Krichieff, Anderson, Small, & Jennings, 1982; Gillberg & Wahlstrom, 1985; Minton, Campbell, Green, Jennings, & Samit, 1982). The concordance rate of parents and children is unknown, as most persons with autism do not have children.

From these studies, one can conclude that there are inherited forms of autism. A classical segregation analysis of 46 multiple-incidence families supported the hypothesis of an autosomal recessive pattern of inheritance for autism (Ritvo *et al.*, 1985). A subset of these multiple-incidence families were subjected to chromosomal linkage analysis with 30 standard phenotypic markers (Spence, Ritvo, Marazita, Funderburk, Sparkes, & Freeman, 1985). No significant linkage was detected with any of the markers used, with the possible exception of the haptoglobin marker (lod score 1.04).

It is possible that autism is a severe form of a broader genetic disorder. Thus, if we look at a wider range of symptoms within these families (such as milder forms of autism, schizoid personality disorders, language disorders, learning disabilities, and mental retardation), a pattern of genetic disease may arise. A few studies have revealed an increased incidence of cognitive deficits in families of autistic persons (August, 1981; Minton, 1982); however, no abnormalities in IQ were detected among the siblings and parents of autistic individuals (Freeman, Ritvo, Mason-Brothers, Pingree, Yokata, Jensen, McMahon, Peterson, Mo, & Schroth, 1989).

Karyotypical analysis of autistic patients reveals that 5%–15% of autistic males and a few females have a chromosomal abnormality of the X chromosome, called *fragile X* (Gillberg, Persson, & Wahlstrom, 1986). The finding of a specific chromosomal abnormality, along with the clear evidence from the inheritance studies, shows that autism can be caused

by genetic defects. At this point, it remains to be seen how many different genes will be implicated in this disorder.

5.1.2. Neuropathology

Findings from autopsies of the brains of autistic subjects have generally been nonspecific. One major problem with neuropathological studies is the inability to control for incidental factors that can affect the structure of the brain, such as seizures, mental retardation, and psychotropic medications (anticonvulsants and antipsychotics). However, a neuropathological abnormality that has been noted in several studies is a decrease in the number of Purkinje and granule cells in the cerebellar vermis and hemispheres (Bauman & Kemper, 1985; Ritvo *et al.*, 1986; Williams, Hauser, Purpura, DeLong, & Swisher, 1980).

5.1.3. Radiology

A variety of radiological imaging studies have been performed on autistic subjects, using computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). The findings of the CT studies have been either negative (Creasey, Rumsey, Schwartz, Duara, Rapoport, & Rapoport, 1986; Damasio, Maurer, Damasio, & Chui, 1980) or nonspecific; nonspecific findings include ventricular enlargement (Campbell, Rosenbloom *et al.*, 1982; Damasio, Maurer, Damasio, & Chui, 1980), asymmetry of ventricles (Prior, Tress, Hoffman, & Boldt, 1984; Damasio *et al.*, 1980, and reverse hemispheric asymmetry with right greater than left (Damasio *et al.*, 1980). The CT scan studies, like the neuropathology studies, have not controlled for mental retardation, seizures, or use of anticonvulsant and antipsychotic medications.

MRI scans have provided exciting data that appear to link alteration in brain structure to autism. Courchesne and co-workers (1987, 1988) have reported MRI studies in which 14 to 18 persons with autism had hypoplasia of two cerebellar vermal lobules (VI and VII), compared to controls. A more recent MRI scan of some of the same autistic persons revealed smaller cerebellar hemisphere size than in normals (Murakami *et al.*, 1989). These studies controlled for the incidental effects of mental retardation, other neurological diseases, and the use of psychotropic medication. These results are consistent with the neuropathological studies described above, in which decreased numbers of Purkinje and granule cells were found in the cerebellum. Courchesne *et al.* hypothesized that damage to the cerebellum may be important in causing the autistic syndrome. This assertion is strengthened by the fact that the

cerebellar vermis has extensive direct and indirect connections with brain-stem and limbic regions that have been implicated in the control of complex behaviors and affects (Berntson & Torello, 1982; Supple, Leaton, & Fanselow, 1987).

A second MRI study of 13 nonretarded autistic subjects found decreased size of the total brain stem, particularly the pons, in persons with autism (Gaffney, Tsai, Kuperman, & Minchin, 1987). Gaffney suggested that the rhombencephalon (which includes the pons and the cerebellum) is abnormal in persons with autism. This study included appropriate controls for mental retardation; one subject had seizures and took anticonvulsants, and two subjects had neurofibromatosis.

Finally, another MRI study found subtle abnormalities in the forebrain of autistic patients (Gaffney, Kuperman, Tsai, & Minchin, 1989). These workers found larger lateral ventricles, larger anterior ventricular horns, and a smaller right lenticular nucleus, suggesting pathology at the cerebral cortical level and in the subcortical gray matter.

Because of the risks arising from exposure to radioactive material, there are very few PET studies of patients with autism. Rumsey and co-workers (1985) studied 10 men with autism and 15 age-matched controls. There was a significant increase in the brain metabolism of glucose in the autistic group during rest. However, there was considerable overlap between the groups. Heh and co-workers (1989) studied the cerebellum of 7 persons with autism and compared them with 8 age-matched controls. The subjects were given a visual vigilance task to perform during a 30-minute PET scan. In this study there was a small but not statistically significant increase in glucose metabolism of the cerebellum in the autistic group. Heh and co-workers recommended repeating the study using a task that involved cerebellar functioning, as MRI studies have recently implicated the cerebellum as a probable locus of defective brain development in autism.

5.1.4. Neuropsychology

Patients with autism have also been studied by means of a variety of neuropsychological methods, including the EEG, dichotic listening, event-related potentials (ERP), and measurements of autonomic and vestibular function. A large body of data encompasses these studies, which are reviewed in greater detail by Ornitz (1985, 1989) and Courchesne (Courchesne, 1987).

Dawson and co-workers (Dawson, Warrenburg, & Fuller, 1982; Dawson, Warrenburg, & Fuller, 1983) found reduced left-hemispheric EEG activity in autistic individuals. Other investigators (Ogawa, Baba, Nadashita, & Hiramatsu, 1979) demonstrated failure of normal hemi-

spheric lateralization in autistic persons; however, this effect was also noted in mental-age-matched controls. This finding suggests that a maturational delay explains the abnormality in autistic individuals.

The results of dichotic listening studies are nonspecific and often contradictory (Wetherby, Koegel, & Mendel, 1981; Hoffman & Prior, 1982; James & Barry, 1983).

In EPR studies, an attempt has been made to determine whether autistic individuals have defects either in the immediate sensory processing that occurs in the brain stem, or in the delayed sensory processing that occurs in the cortex. Courchesne (1987) reviewed the research criteria necessary to obtain reliable and interpretable ERP data. These criteria were not implemented in many ERP studies. For the studies that do meet these criteria (Novick, Vaugn, Kurtsberg, & Simon, 1980; Courchesne, Kilman, Galambos, & Lincoln, 1984; Courchesne, Lincoln, Kilman, & Galambos, 1985; Dawson, Finley, Phillips, & Galpert, 1986) Novick, Kurtsberg, & Vaughan, 1979; the results are reviewed here. Most of these studies have focused on the auditory system, some on the visual system, and, at this time, none on the somatosensory system.

Early EPR waves (I-V) are the evoked potentials of the auditory sensory pathways in the brain stem. These waves are commonly referred as *brain-stem auditory evoked responses* (BAER). There is no difference in the EPR waves (I-V) in autistic individuals and in controls. Thus, there is no primary auditory defect in autism. A significant finding is a reduction in the P300 wave amplitude in autistic individuals compared to controls. The P300 wave is one of the waves that represent secondary sensory pathways in the cortex and is the component associated with attention to event importance. This finding is suggestive of a defect in secondary processing in autistic individuals or a defect in systems that affect these secondary processes.

Studies of the autonomic system have shown increased heart-rate variability among persons with autism (MacCulloch & Williams, 1971; James & Barry, 1980) particularly during stereotypical behavior (Hutt, Forest, & Richer, 1975). Vestibular studies are limited by technical difficulties such as failure to control for visual fixation. Ornitz (1985) controlled for visual fixation by lacing the subjects in absolute darkness. This study revealed "prolonged time constants in the autistic group [which] suggest dysfunction of a multisynaptic path in the BSRF (brain-stem reticular formation) in the autistics, a path that might involve reverberating neuronal circuits."

5.1.5. Neurochemistry

The body of information linking abnormal neurochemical functioning to infantile autism has been generally inconclusive. Although indi-

vidual studies have occasionally, sometimes repeatedly, observed abnormal levels of neurotransmitters or their metabolites in autistic subjects, none have been unequivocally or uniquely linked to autism. We recently reviewed the literature in this area (Elliott & Ciaranello, 1987), and so we only highlight the topic here.

5.1.5.1. Serotonin. Interest in serotonin and autism developed with the discovery by Schain and Freedman (1961) that some autistic individuals have elevated blood serotonin. That report and many others have demonstrated that about one third of autistic individuals and about one half of retarded children have elevated blood serotonin. Efforts to elucidate the mechanism of hyperserotonemia or its metabolic and developmental significance have been unsuccessful. Lowering elevated serotonin in autistic children with fenfluramine or other agents has not had a dramatic impact on autistic behaviors.

5.1.5.2. Dopamine. There has been great interest in dopaminergic dysfunction in schizophrenia. There have been reports of elevated levels of the dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid of some autistic individuals (Cohen, Caparulo, Shaywitz, & Bowers, 1977). However, these reports have not correlated with autistic symptoms or behaviors.

5.1.5.3. Norepinephrine. Central noradrenergic systems have been implicated in a wide range of normal and abnormal behaviors and brain functions, but there is little evidence to link them with autism. Plasma norepinephrine has been reported to be elevated in autistic subjects (Lake, Ziegler, & Murphy, 1977). This same group reported that dopamine β -hydroxylase (DBH), the terminal enzyme in norepinephrine biosynthesis, was decreased in the blood of autistic subjects, but this finding has not been uniformly replicated. With the recent cloning of the cDNA for human DBH (Lamouroux, Vigny, Faucon-Biquet, Darmon, Frank, Henry, & Mallet, 1988) and the mapping of the DBH gene to chromosome 9, interest in this enzyme as a possible linkage marker in autism has been rekindled.

5.2. Etiologies of Autism

Many neurological disorders are associated with autism. Some are relatively well-understood diseases, such as PKU, in which the genetic origin of the disease is identified. In other disorders, such as Rett's syndrome, neither the genetic origin nor the pathophysiology is understood. In studying a range of autism-associated neurological disorders, we expect to learn more about the etiology of autism. A complete list of these disorders is given in Table 2. The association between many of these neurological disorders is given in Table 2. The association between these neurologic disorders and autism is weak and consists of many of these neurologic disorders and autism is weak and consists of

TABLE 2
Neurological Disorders
Associated with Autism

Genetic disorders
Tuberous sclerosis
Neurofibromatosis
Möbius syndrome
Fragile X
Phenylketonuria
Birth injuries
Rett syndrome
Infections
Congenital rubella
Cytomegalovirus
Toxoplasmosis
Syphilis
Varicella
Herpes
Mumps

only a few case reports (i.e., herpes encephalopathy, CMV infection, toxoplasmosis, neurofibromatosis, and tuberous sclerosis).

5.2.1. Fragile X

Fragile X (Martin-Bell syndrome), a sex-linked disorder, is the most common disorder associated with autism. The clinical syndrome, first described by Martin and Bell (Martin & Bell, 1943), usually includes a combination of dysmorphic facies, mental retardation, and enlarged testicles. The name *fragile X* refers to the characteristic chromosomal marker, a fragile site on the long arm of the X chromosome (Xq27) (Lubs, 1968). This fragile site is identifiable only when cells are grown in folate-deficient culture medium (Sutherland, 1977). The estimated incidence of fragile X syndrome is 1 in 1,000 to 1 in 2,000 live male births (Turner & Jacobs, 1983; Herbst & Miller, 1980). Because autism occurs in only 1 in 10,000 live births, it is obvious that only a very small minority of fragile X-syndrome individuals are autistic.

Fragile X is the second most common genetic cause of mental retardation, Down syndrome being the first. Blomquist and co-workers (Blomquist, Gustavson, Nordendson, & Palsson-Strae, 1983; Blomquist, Bohman, Edvinsson, Gillberg, Gustavson, Holmgren, & Wahlstrom, 1985) estimated that 4%–7% of children with mental retardation had fragile X syndrome. The clinical presentation of fragile X syndrome is variable. Usually, individuals with this disorder have cognitive deficits

ranging from mild to severe mental retardation. They have a thin and elongated face, a prominent mandible, and enlarged and poorly developed ears. After puberty, boys develop enlarged testicles. Female carriers are usually normal; however, some exhibit cognitive deficits in addition to dysmorphic facies (Veenema, Geraedt, Beverstock, & Pearson, 1987; Turner, Brookwell, Daniel, Selikowitz, & Zilbowitz, 1980). Many children with fragile X develop various behavioral abnormalities, including hyperactivity, attention deficits, and autistic behaviors.

The association of fragile X and autism is well documented (Watson, Leckman, Annex, Breg, Boles, Volkmar, & Cohen, 1984; McGillvray, Herbst, Dill, Sandercock, & Tischler, 1986; Blomquist, Bohman, Edvinsson, Gillberg, Gustavson, Holmgren, & Wahlstrom, 1985; Blomquist, Gustavson, Nordendson, & Palsson-Strae, 1983; Gillberg & Wahlstrom, 1985; Turner, Brookwell, Daniel, Selikowitz, & Zilbowitz, 1980). These authors have found that 0%–25% of autistic persons have fragile X syndrome, the higher percentage being found in institutionalized populations. The association between these disorders is so strong that the term AFRAX, referring to "autism-fragile-X syndrome," has been coined (Gillberg, Persson, & Wahlstrom, 1986). Although most studies of autism associated with fragile X have concentrated on males, Gillberg and co-workers (Gillberg, Ohlson, Wahlstrom, Steffenburg, & Blix, 1988) reported on a single pair of monozygotic twin girls. Both twins had autism and fragile X syndrome.

There have been a few neurobiological studies on fragile X syndrome. Veenema and co-workers (1987) studied a large family with 18 fragile-X-positive men. CT scans were done on 3 of the 18, and all scans showed ventricular enlargement. Autopsy findings on a 62-year-old man with fragile X were remarkable for microscopic changes in the neocortex, an abnormal dendritic spine pattern (thin, long, and tortuous spines), and a decreased mean synaptic length (Rudelli, Brown, Wisniewski, Jenkins, Laure-Kamionowska, Connell, & Wisniewski, 1985). These abnormalities are also found in persons with trisomic chromosomal disorders; thus, they are not unique to fragile X. The cerebellum was not mentioned in this study, and so it is unclear whether the cerebellum was studied. A preliminary MRI study revealed a decrease in the size of the pons and the posterior cerebellar vermis in four men with fragile X syndrome compared to controls (Reiss, Patel, Kumar, & Freund, 1988). Because only two of the four men in this study had autism, it seems clear that not all posterior cerebellar vermal defects produce autism.

The developmental links between the fragile X gene(s) and the clinical disorder is unknown. However, it seems likely that one or more genes linked to the fragile X site on the long arm of the X chromosome

may be critical for normal development of the brain. This gene may well be one of the neurodevelopmental genes described earlier. The gene or genes may encode some protein essential to the normal development of specific structures in the brain.

5.2.2. Phenylketonuria

Phenylketonuria (PKU) is an example of a metabolic disease that is associated with autism. Infants with PKU are normal at birth and, if untreated, will develop mental retardation during the first year of life. Other clinical features of untreated children include light hair and skin, eczematoid dermatitis, and self-injurious behavior (e.g., arm biting and head banging). In addition, some children develop autistic behaviors and seizures. PKU is caused by a genetic defect that results in a deficiency of the enzyme phenylalanine hydroxylase. This enzyme converts the amino acid phenylalanine into the amino acid tyrosine. Without this enzyme, the total body concentration of phenylalanine and other metabolites increases to toxic levels. Children with PKU are treated with a diet phenylalanine and other metabolites. Children with PKU develop normally if they are started on a special diet soon after birth. In the United States, all infants are screened for PKU, and so very few children go untreated.

Phenylketonuria is inherited as an autosomal recessive disorder with an incidence of 1 in 14,000. The carrier rate is 1 in 60. Friedman (1969) reviewed various studies that identified a group of children with PKU who were autistic, in addition to their mental retardation. Lowe and co-workers (Lowe, Tanaka, Seashore, Young, & Cohen, 1980) studied 65 children with autism and identified three children with PKU who had not been diagnosed in infancy. Thus, PKU unfortunately continues to be a cause of autism.

PKU offers an opportunity to study the relationship of autism to mental retardation. When treatment was first available for PKU, many children were treated late in childhood, after the development of mental retardation and autism (Friedman, 1969). Children who initially presented with both mental retardation and autism showed significant improvement in their autistic behaviors and no change in their intellectual abilities when started on a phenylalanine-free diet. Interestingly, when the diet was discontinued, the autistic behaviors recurred. Thus, changing the concentrations of phenylalanine and its metabolites had an effect on the severity of autistic behaviors in children with PKU. In this instance, then, autism can be clearly separated from mental retardation.

Before birth, the fetus was PKU develops normally because the

excess phenylalanine is metabolized by the maternal enzyme. Non-PKU infants who are born to mothers with PKU are exposed to high concentrations of phenylalanine during fetal development. These children develop a syndrome consisting of microcephaly, mental retardation, and structural defects such as cardiac anomalies (Mabry, Denniston, Nelson, & Son, 1963).

As there are few children with untreated PKU, the number of neurobiological studies are few. An autopsy study on a 27-year-old man with both PKU and autism revealed a reduced density in dendritic spines of pyramidal neurons in the cortex, a finding also present in one other autistic person (Williams, Hauser, Purpura, DeLong, & Swisher, 1980). A reduction in the number of Purkinje and granule cells was induced in the cerebellum of sucking rats after a toxic level of phenylalanine was injected into the rats (Huether, Neuheoff, & Kaus, 1983).

5.2.3. Congenital Rubella

Children with congenital rubella are, by definition, infected with rubella virus early in prenatal development. As a result of this infection, many organ systems are affected, and the infants are born with a variety of congenital malformations, including deafness, blindness, heart disease, skeletal deformities, and central nervous system (CNS) abnormalities. The CNS abnormalities range from mild cognitive defects to severe mental retardation, in addition to various deviant behaviors and seizures. The incidence of this disease has dropped significantly since the development of the rubella vaccine. The most recent large population studies occurred in 1964, during the last epidemic. Two studies reported a significant incidence of 8%–13% of children with congenital rubella who were autistic (Desmond *et al.*, 1967; Chess, 1977).

Desmond, Wilson, Melnick, Singer, Zion, Rudolph, Pineda, Ziai, and Blattner (1967) reported on neuropathological studies done on 13 infants who died of congenital rubella. Of the 13, 11 had CNS abnormalities consisting of widely distributed focal areas of cell death, glial proliferation, and vasculitis. Although the focal areas of cell death were distributed throughout the brain tissue, more were found in the basal ganglia. Desmond and co-workers did not describe the neurological symptoms in these 13 cases, except to state that all but 2 had clinical evidence suggestive of CNS involvement. Although none of these children lived long enough to develop autism, the neuropathological findings are representative of the type of brain damage to be expected in congenital rubella.

5.2.4. *Rett Syndrome*

Rett syndrome is characterized by a variety of symptoms: mental retardation, autistic behaviors, gait abnormalities, seizures, respiratory symptoms such as hyperventilation, and peculiar stereotypical hand movements such as hand wringing (Naidu, Kitt, Wong, Price, Troncoso, & Moser, 1988). To date, this syndrome has been identified only among girls. It is a neurodegenerative disorder that clinically presents between the ages of 6 and 18 months. Children regress both motorically and cognitively. Between 1 and 3 years of age, children with Rett syndrome lose purposeful hand use as they develop stereotypical hand movements. Rett syndrome was first described by Rett in 1966. The incidence is estimated to be between 1 in 10,000 and 1 in 15,000 females.

The etiology of this syndrome is unknown, but as for autism, there have been many genetic and neurobiological studies. Rett syndrome is considered to be a sex-linked dominant condition, lethal in males, with sporadic new mutations (Comings, 1986). Affected females do not reproduce. Neuropathological studies have revealed nonspecific findings of diffuse cerebral atrophy with microcephaly, mild cortical atrophy, mild astrocytic gliosis, and mild spongy changes. One specific finding was a decreased pigmentation of cells within the substantia nigra nucleus (these cells are dopaminergic and project to the basal ganglia) (Jellinger *et al.*, 1988; Naidu *et al.*, 1988). A biopsy of the right frontal lobe of a 6-year-old girl with Rett syndrome revealed membrane-bound inclusions in both neurons and oligodendrocytes when the tissue was viewed by electron microscopy (Papadimitriou, 1988). Systematic studies of the cerebellum and Rett syndrome have not been reported.

5.3. *Summary*

In this section we have reviewed the major known etiologies of autism and have described the neuropathological changes found in the brains of a number of affected individuals. Autism is clearly caused by abnormalities in brain development. Although recent studies showing that the cerebellum and the brain stem are abnormal in many autistic patients are extremely exciting, it is premature to conclude that damage to these regions of the brain cause autism. Given the wide variety of the etiologies of autism, it is likely that several different neuropathological mechanisms lead to this syndrome.

6. *Conclusions*

In this chapter, we have reviewed three subjects. First, we described the basic elements of brain development. Much of early develop-

ment follows a genetic blueprint; the genes direct biochemical and biophysical processes that assemble the brain. Then, once sensory pathways are constructed, these pathways convert environmental information into physiological signals; these signals then lead to changes in synaptic connections. Therefore, abnormalities in either the genetic information or the ability to detect and process environmental information can cause the ability to detect and process environmental information or the ability to detect and process environmental information can cause defects in brain development. Furthermore, there are large numbers of toxins, microorganisms, and other environmental hazards that can seriously disrupt normal development.

In Section 3, we reviewed the major categories of mammalian developmental neuropathological abnormalities. Work in this area is beginning to provide some clues to the relationship of damage to particular structures and its effect on cognition and behavior. Furthermore, this work will aid in the identification of additional etiologies.

In Section 5, we described some of the etiologies of autism and their associated neuropathology. At present, there are exciting results that are linking abnormal development of the cerebellum to this syndrome. Although it is premature to conclude that autism is caused by cerebellar pathology, these results provide an important framework within which to further explore the basis of this disease.

Although we have limited ourselves to describing autism, we and other workers believe that most neuropsychiatric disorders of childhood have a biological basis. Mental retardation, specific learning disorders (Duane, 1989), attention deficit disorder (Zametkin & Rapoport, 1987), childhood schizophrenia, and Tourette disease are caused, at least in part, by abnormalities in the development of the brain. Given that about 50,000 different genes are specifically expressed in the brain (Hahn *et al.*, 1986), one can imagine that there might be a large number of different mutations that lead to neuropsychiatric disease. Furthermore, there are probably unknown environmental hazards that cause abnormalities in brain development and that need to be identified. Finally, more study needs to be done to ascertain the effects on infants and children of psychological trauma and neglect.

Therefore, we are still just beginning to understand the causes of the neuropsychiatric disorders of childhood. Some of these disorders can be prevented by avoiding exposure to environmental hazards. Genetic counseling and prenatal diagnosis are also important methods of preventing these illnesses. At present, the treatment modalities are generally limited to empirical psychopharmacological agents, which, at best, ameliorate the symptoms, without treating the underlying disease. Optimal treatments will require that we understand the molecular basis for these disorders. The challenge for the future will be to apply

basic neurobiology and genetics to unravel the causes of these tragic illnesses.

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The Neurobiology of Developmental Disorders

JOHN L. R. RUBENSTEIN, LINDA LOTSPEICH, AND
ROLAND D. CIARANELLO

From: *ADVANCES IN CLINICAL CHILD PSYCHOLOGY*, VOL. 13
Edited by Benjamin B. Lahey and Alan E. Kazdin
(Praeger Publishing Corporation, 1990)

1. Introduction

Developmental disorders affecting intelligence and behavior are among the most mystifying diseases of humankind. This is because they are primarily caused by abnormalities in the development of the most complex human organ, the brain. Perhaps the reason so little is understood about mental retardation, autism, childhood schizophrenia, attention deficit disorder, specific learning disorders, and Tourette disorder is that very little is still understood about how a normal brain develops. The premise of this chapter is that the key to understanding these illnesses is an understanding of the processes involved in neurodevelopment.

In the first section, we describe the basic processes involved in brain development. This discussion serves as a foundation for the next section, in which we review the major pathological disorders of the developing nervous system. In the final section, we examine the biological basis for the syndrome of autism. We have chosen to focus on autism because its etiology is clearly biologically based, and because of a series of recent neuropathological findings that are providing some clues about the neurobiological basis of this disorder.

2. Neurobiology of Brain Development

This section describes how the brain is assembled during the development of a mammalian embryo. Some of what is described are results from animals other than humans. However, to date, there is no reason to

JOHN L. R. RUBENSTEIN, LINDA LOTSPEICH, AND ROLAND D. CIARANELLO, Department of Psychiatry, Division of Child Psychiatry, Stanford Medical School, Stanford, California 94305.

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3793

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

April 1, 1991

Dear Enid,

Thank you for your letter of March 15, 1991, enclosing your recent article on biologically-based brain disease and the chapter by Roland Ciaranello. I have forwarded a copy of your letter to Roger Porter, so that the Subcommittee on Brain and Behavioral Science may consider your suggestion for a national conference on biologically-based brain disease in children and adolescents.

Best regards to both you and Richard.

Sincerely yours,



D. Allan Bromley, Ph.D.
Director

Enid Peschel, Ph.D.
Co-Director, Program for
Humanities in Medicine
Assistant Professor (Adjunct)
Department of Internal Medicine
Yale University School of Medicine
8 Country Club Drive
Woodbridge, Connecticut 065256

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

April 1, 1991


Dear Dr. Porter:

Enclosed please find a letter from Dr. Enid Peschel. The Subcommittee on Brain and Behavioral Sciences may wish to consider her suggestion regarding a national conference on biologically-based brain disease in children and adolescents as part of activities planned during the Decade of The Brain.

Sincerely yours,



D. Allan Bromley, Ph.D.
Director

Enclosures

Dr. Roger Porter
Chairman, Subcommittee on
Brain and Behavioral Sciences
Deputy Director
National Institute of Neurological
Disorders and Stroke
National Institutes of Health
Building 31, Room 8A52
Bethesda, Maryland 20892

"CORRESPONDENCE TRACKING"

TYPE: Action Item

DOCUMENT NUMBER: 9120795

FROM: McDEERFIELD, Warren; Coral Gables, FLA

TO: DAB

DATE OF
CORRESPONDENCE: 03/14/91

SUBJECT: Thoughts on Stress and Aging Process

ASSIGNED TO: D.A. Henderson

ACTION REQUIRED: Necessary Action

SENDER'S DUE DATE: OSTP DUE DATE: 04/01/91

DATE COMPLETED: 03/20/91

COPIES TO: Rachel Levinson
Alicia Dustira

WHITE HOUSE TRACKING #: CONTACT PERSON:

REMARKS:

DATE RECEIVED: 03/18/91
DATE RECEIVED DLS: 03/19/91

FILE: ~~DLS--AGING~~
P- Life Sciences

██████████

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

March 20, 1991

Dear Mr. McDeefield:

Dr. Bromley asked that I reply to your thoughtful letter. I believe you would be best advised to be in contact with the National Institute on Aging, National Institutes of Health, Building 31, Room 2C02, Bethesda, Maryland 20892, whose director is Dr. T. Franklin Williams. Stress and its alleviation is a most important topic to which they devote a great deal of attention.

Thank you for your thoughts.

Sincerely yours,

A handwritten signature in dark ink, appearing to read 'D. A. Henderson', with a stylized, flowing script.

D. A. Henderson, M.D., M.P.H.
Consultant

Mr. Warren McDeefield
19 Antilla Avenue
Coral Gables, Florida 33134

9120795

RECEIVED

19 Antilla Avenue
Coral Gables, Florida 33134
Daytime telephone: (Collect)
305-751-3762

91 MAR 18 P 5: 07

OFFICE OF THE
DIRECTOR

Doctor D. Allan Bromley
Presidential Senior Science Advisor
The White House
Washington, D. C. 20202

Dear Dr. Bromley:

In a letter I wrote to the Secretary of State in June (this was about another matter) I made notice of my efforts to promote gerontological research whereas I should have written to you should I have known then who to write to. I telephoned your office several times since then and finally was able to acquire the exact spelling of your name (considering my interest in a new science) and your function, which an operator was able to figure out considering my request when I originally telephoned months ago.

This is a purely scientific matter to which I want to ask your advice for further research through the National Institutes on Aging (still in Bethesda?) with my association with the former assistant to clinical research of the Federal Government (now teaching in California). The last time I spoke to this gentleman--actually the only time--the rest was correspondence, I promised him I was on my way to the White House (the original Conferences On Aging started, I believe, in 1972--and it as in 1981 that a clerk there referred me to this gerontologist) but I was only going on a tour December 8, 1990. On that day, a Friday, I was told by a guard that it was closed for conferences and decorating. Was I supposed to wait for someone to write or approach me first? (because I telephoned ahead). Strangely enough the best part of my first and only trip to the Capitol was the tour I took after my arrival to your buildings when a Secret Serviceman gave me a map (he was on a "golf cart") which made my trip otherwise perfect! I still cherish this and perhaps you can check your log of about 10:30 A. M. that day and personally thank him. Next time I guess I will go on regular tour and get in touch with you elsewhere if it is better suited for you sir.

As you probably already know it is a known fact that the Methusalah Syndrome is what causes the aging process in human beings. Originally I contended with the former assistant researcher of the NIA that this phenomenon (na) was due to gravity in connection to biorhythms and its debilitating effects on the body but more recently I, upon observation conclusively believe this process is due mostly to the same debilitating effect of stress on the system. In other words if we could somehow program our brains to eliminate the phenomena called stress, life could be extended considerably longer, if not indefinitely, if we were to fully understand this process.

(continued)

Dr. Bromley I would sincerely appreciate it if you would please share any ideas, comments or suggestions about this always sought after topic, its present level of activity in the Federal Government, local or state or through the private sector though your function is through the NIA. A tour of the latter (Pass) may be best.

A full response to all of the the above would be best.

Waiting to hear from you I remain,

Yours most sincerely,

Warren Mc Neufeld

March 14, 1991

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION

DOCUMENT NUMBER: 9120550

FROM: MOSSINGHOFF, Gerald J.: PHARMACEUTICAL MANUFACTURERS ASSOCIATION

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 02/27/91

SUBJECT: A REPORT ON "ORPHAN DRUGS IN DEVELOPMENT"

ASSIGNED TO:

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO: D. Allan Bromley
Ken Yale
Life Sciences

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS: Dr. Bromley received the enclosure.

DATE RECEIVED: 02/27/91

FILE: *P*- LIFE SCIENCES

9120550

**Pharmaceutical
Manufacturers
Association**

Gerald J. Mossinghoff
PRESIDENT

RECEIVED

91 FEB 27 AM 11:44

OFFICE OF THE
DIRECTOR
February 27, 1991

Mr. D. Allan Bromley
Assistant to the President for
Science and Technology
Old Executive Office Building
725 17th Street, N.W.
Washington, D.C. 20506

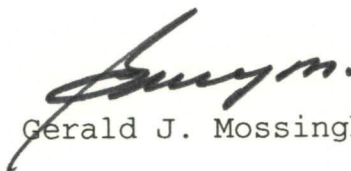
Dear Allan:

Enclosed is a report of our latest survey on "Orphan Drugs in Development". It shows that 176 medicines are now being tested in humans for rare diseases. The report also lists the 54 rare disease treatments that have been approved by the Food and Drug Administration under the Orphan Drug Act of 1983.

These survey results, which PMA is announcing at a 9:30 a.m. press briefing this morning, illustrate the extraordinary success of the orphan drug program.

If you would like additional copies of the report, please call Judee Shuler at (202) 835-3467.

Sincerely,



Gerald J. Mossinghoff

Enclosure

—IN DEVELOPMENT— —ORPHAN DRUGS—

Presented by the Pharmaceutical Manufacturers Association

1991 Annual Survey

176 Medicines in Testing for Rare Diseases

A record number of orphan drugs are in development to treat rare diseases, according to a survey by the Pharmaceutical Manufacturers Association. The survey shows that 176 orphan drugs are in development compared to 133 in 1989.

Under the Orphan Drug Act of 1983, the Food and Drug Administration has granted 422 orphan drug designations as of February 12, 1991. Such status, granted before the drug is approved for marketing by the FDA, entitles sponsors to certain incentives to develop drugs for rare diseases.

The most important of these incentives is seven years of marketing exclusivity following FDA approval of the drug. This helps sponsors recover the substantial sums spent on research and development, which would be difficult otherwise, because orphan status is granted to drugs that treat diseases with a patient population of 200,000 or less.

In fact, most orphan drugs are being developed to treat diseases that afflict far fewer than 200,000 people. According to a report by the U.S. Department of Health and Human Services Orphan Products Board, 56 percent of the orphan designations in 1989 were for diseases with a patient population of 50,000 or less and 31 percent were for diseases affecting less than 25,000 people.

Other findings in our survey are:

- Some important areas of orphan drug research include: AIDS and AIDS-related conditions with 24 drugs in development, cancers with 54, childhood diseases with 46, diseases of women with 12, genetic disorders with 31, and neuromuscular disorders with 11. More details on the orphan drugs in development in these areas is provided in the table on page 2.

- Some of the 176 orphan drugs have been designated by FDA for more than one rare condition, resulting in a total of 234 orphan designations. Each designation along with the name of the drug, its development status and the drug's sponsor are listed, beginning on page 3 of this report. All drugs listed under the heading "Orphan Drugs in Development" are either in human clinical trials or have an application for marketing at the FDA for review.

- Of the 234 orphan drug designations, 50 are awaiting approval at the FDA, compared with 40 in 1989, and 86 are in the final stage of development, 22 more than in 1989.

- Developing these drugs are 104 companies and 16 other sponsors. Many of these are smaller companies.

To add to the value of this report, this year we have also included a list of the orphan drugs that have been approved since the Orphan Drug Act was passed in 1983.

Since then, 54 orphan drugs have been approved to treat 60 rare disease conditions, an increase of 18 drugs approved since August of 1989. They can be found listed under "Approved Orphan Drugs" beginning on page 15.

Our PMA Commission on Drugs for Rare Diseases continues to play an important role in encouraging orphan drug development by helping individual researchers find corporate sponsors for promising therapies. More information on the Commission's work is provided in an article on the back page of this report.

Both the work of the Commission and the contents of this survey report exemplify the leadership role that America's research-based pharmaceutical industry is taking in orphan drug research. Each year since the Orphan Drug Act was passed in 1983, more drugs for rare diseases are being developed and approved for use. Despite this, we must not lose sight of what remains to be done. Most of the 5,000 known rare diseases remain untreated. We have by no means achieved our goals until new drugs are available for each and every one of them.



Gerald J. Mossinghoff
President

Pharmaceutical Manufacturers Association

The PMA is grateful to the FDA's Office of Orphan Products Development for their assistance in producing this survey report and to the 30 organizations that are presenting this information in cooperation with the PMA. They are listed on the back of this report.

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION

DOCUMENT NUMBER: 9120629

FROM: GLASER, Robert J.: LUCILLE P. MARKEY CHARITABLE TRUST

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 02/26/91

SUBJECT: A THANK YOU LETTER FOR COMMENTING ON THE LETTER DR.
GLASER SENT TO DAVE PACKARD.

ASSIGNED TO:

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED: -----

COPIES TO: D. Allan Bromley
Life Sciences

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 03/04/91

FILE: *P*- LIFE SCIENCES- BIOMEDICAL

22-211101

LUCILLE P. MARKEY CHARITABLE TRUST

MIAMI, FLORIDA

RECEIVED

91 MAR 4 P2:41

OFFICE OF THE
DIRECTOR



525 MIDDLEFIELD ROAD, SUITE 130
MENLO PARK, CALIFORNIA 94025
(415) 323-6700

ROBERT J. GLASER, M.D.
TRUSTEE AND
DIRECTOR FOR MEDICAL SCIENCE

February 26, 1991

Dr. D. Allan Bromley
Assistant to the President for
Science and Technology
The White House
Washington, D.C.

Dear Dr. Bromley:

You were very kind indeed to take time from your busy schedule to comment on the letter I had sent to Dave Packard at his request in November. I am very well aware that nothing I said in my letter would have come as a surprise to you because I know how seriously you have worked to enhance support for all of the components that are so essential to research.

In accordance with the donor's wishes, the Markey Trust has devoted all of its resources to the support of basic biomedical research. Mrs. Markey directed that the foundation give away all of its assets within fifteen years of her death, and inasmuch as she died in 1982, we will be going out of business in 1997. Given the terms of the Trust, we have been giving away both income and principal; we have utilized our funds to support major new investigative initiatives as well as to fund the Markey Scholar Program, which each year has provided very bright young senior postdoctoral men and women with six to eight years of support. The program is not too different from that which you know at the Packard Foundation. As a matter of fact, up to now I have been unable to attend any of the Packard Fellow meetings because they have coincided with the annual meeting of the Markey Scholars but I had the foresight to change the arrangement for the coming year, and I look forward to being present, and I hope to have a chance to see you in person.

It is almost fifty years since I graduated from medical school; I spent the first half of my professional life in academia and have been involved in medically-oriented philanthropy since. When I see the enormous progress we have made, I find it hard to

Dr. D. Allan Bromley
February 26, 1991
Page two

believe, and I am also painfully aware of the fact that without modern instrumentation and facilities, even the most gifted scientist is apt to be left in the lurch. In my early years, when I used to spend a good amount of time as an NIH consultant, funding was plentiful, and as I look back on those years, I realize how much easier it was to run a scientific enterprise than it is today.

Be that as it may, it is fortunate that you are in the position you are in, and despite all the obstacles, I think scientists across the country recognize the debt they have to you for your leadership.

Thank you again so much for having taken the trouble to write. With all warm regards, I remain

Very sincerely yours,

Robert J. Glaser (m)
Robert J. Glaser, M.D.

Dictated by Dr. Glaser;
signed in his absence.

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION

DOCUMENT NUMBER: 9120584

FROM: PESCHEL, Enid: YALE UNIVERSITY, THE SCHOOL OF MEDICINE

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 02/25/91

SUBJECT: BIOLOGICALLY-BASED BRAIN DISEASES.

ASSIGNED TO:

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO: D. Allan Bromley
Life Sciences

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS: *Publication to Life Sciences*

DATE RECEIVED: 03/01/91

FILE: *P*- LIFE SCIENCES BIOLOGY



YALE UNIVERSITY
THE SCHOOL OF MEDICINE



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Program Director

Enid Peschel
Co-Director

Kenneth Kashkin
Assistant Director

Nance Cunningham
Program Coordinator

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THE PROGRAM FOR HUMANITIES
IN MEDICINE

P.O. BOX 3333
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MAILING ADDRESS:

8 Country Club Drive
Woodbridge, Connecticut 06525
February 25, 1991

OFFICE OF THE
DIRECTOR

D. Allan Bromley, Ph.D.
Assistant to the President for Science and Technology
The White House
Washington, D.C. 20506

Dear Allan:

It was very good seeing you and hearing you speak at Yale. Your insights from your years of science research and teaching, plus your experiences as President Bush's science advisor, help put many things--past, present and future--in perspective. It is most enlightening.

I also appreciate your letter of January 18, in which you told me that you have shared our thoughts on the Decade of the Brain with Dr. Roger Porter, Chairman of the Subcommittee on Brain and Behavioral Sciences of the Federal Coordinating Council for Science, Engineering and Technology.

I was glad to be able to tell you that *Biologically-Based Brain Disease in Children and Adolescents*, the book that I am collecting and editing with Dick and with Jim and Carol Howe of NAMI, is scheduled for publication early in 1992 (by Jossey-Bass, in the New Directions for "Mental Health" Services series of sourcebooks). It will begin with chapters by some of the leading neuroscience researchers in child and adolescent psychiatry writing in non-technical language about the biological underpinnings of these biologically-based brain diseases (BBBD). There will be one chapter on each neurobiological disease (e.g. schizophrenia, bipolar disorder, pervasive developmental disorder, etc.). Among the neuroscientists writing chapters for our book are **Fred Goodwin, M.D.**, of ADAMHA; **Jim Leckman, M.D.** of Yale; **Joseph Coyle, M.D.**, of Johns Hopkins; **Roland Ciaranello, M.D.** of Stanford; **Judy Rapoport, M.D.**, of the NIMH.

We are very grateful for your efforts to help infuse science into the field of psychiatry. In line with our work in that direction, I am enclosing the second issue of **NAMI CAN NEWS**, which I edit. This is the national newsletter and ongoing resource manual of the National Alliance for the Mentally Ill Children and Adolescents Network (NAMI CAN). You will enjoy our editorial, "Prospective, Retrospective, and Anecdotal Data: A Demand for Science in Child Psychiatry."

I am also enclosing a copy of a letter that I have sent to Fred Goodwin, M.D., Administrator of ADAMHA, and to Alan Leshner, Ph.D., Acting Director of the NIMH, applauding the NIMH decision to put CASSP (Child and Adolescent Service System Program) under a new division that will seek to scientifically evaluate services to the severely mentally ill. But in my letter I have criticized the language of the current CASSP-NIMH terminology that lumps together under the non-scientific rubric of "severely emotionally disturbed" children and adolescents who have (a) biologically-caused illnesses (the biologically-based brain diseases--**BBBD**--called "mental" illness, including, for example, schizophrenia, bipolar and unipolar disorders, autism, pervasive developmental disorder, obsessive-compulsive disorder, Tourette's disorder, anxiety and panic disorders, attention deficit disorder, hyperactivity, attention deficit hyperactivity disorder) with (b) sociologically- or environmentally-caused "mental health" problems (e.g. abuse, neglect, crime, poverty; neurotic, emotional, psychological, or life-adjustment issues). In light of the past 10 years of neuroscience and basic science research--a good amount of which has been done at the NIMH--it is scientifically unacceptable to continue to lump together people with biologically-caused disorders (BBBD) and people with sociologically- or environmentally-caused "mental health" (i.e. psychological) problems.

We want to do all that we can to infuse science into psychiatry and to help the non-scientific public understand that the severe chronic neurobiological diseases called "mental" illness are, in fact, biological, and not "psychological" or "mental health" problems.

Keep up your most important and enlightening work! Dick joins me in sending you our warmest good wishes.

Sincerely yours,



Enid Peschel, Ph.D.
Co-Director, Program for Humanities in Medicine
Assistant Professor (Adjunct), Department of Internal Medicine
Yale University School of Medicine
PHONE: (203)-397-9269

YOU CAN MAKE THE DIFFERENCE

If the number of calls I have received from parents around the country in the past 3 months is any indicator of the recent growth of NAMI CAN—the National Alliance for the Mentally Ill Children and Adolescents Network—we are INCREASING EXPONENTIALLY! I understand from both Ron Norris, our NAMI Board Liaison, and the NAMI office staff that NAMI's new 1-800 HELPLINE (1-800-950-NAMI) is bringing in literally *thousands* of calls each week.

Many parents who phone me ask the same question: "*How do I get an active NAMI CAN group going that really advocates for improved services to children and adolescents with brain disorders?*" I don't profess to be an expert, but I am pleased to offer my experiences that led to the success of New Mexico's NAMI CAN organization known as "Parents for Behaviorally Different Children" (PBDC).

There is always debate about the name for our "CAN" organizations. Choosing your group's name is a decision that may, or may not, affect your membership. Some veteran NAMI members think that all NAMI affiliates should use the NAMI name. But because PBDC was founded before we knew that NAMI existed, we have kept our original name. Many of our supporters feel that PBDC is easier for young families to accept. Of course, our brochure proudly announces that we are a NAMI CAN affiliate. And as

PBDC parents learn more about our CAN advocacy, the name becomes less important than our work.

If you are a parent wishing to start a CAN organization in your state, it is important to realize that initially a great deal of the work will fall on your shoulders. Recognizing this, and being willing to assume that responsibility, can be very rewarding.

First, you need to find a meeting place and to send out letters to inform people about your group. Good places to start are your Special Education Department and the principal of your child's school. Your first letter can be very brief. You can say that you are a parent of a child who has a behavioral (or a brain) disorder and that you would like to meet with other parents who share some of your frustrations and concerns about their children. On the bottom of your letter, you can ask interested parents to list their names, phone numbers, and meeting times that would be convenient for them.

Your NAMI CAN group will begin with only one parent: YOU! But I am confident that at least ONE other parent will respond. Call that parent and arrange to meet. Talk about what you know best: your children. Plan a second meeting. Send out a second notice. As others learn about your group, they will join in. The first few months you will have to phone parents to remind them about

see DIFFERENCE—cont. page 3

PROSPECTIVE, RETROSPECTIVE, AND ANECDOTAL DATA: A DEMAND FOR SCIENCE IN CHILD PSYCHIATRY

Prospective = forward-looking, future
Retrospective = looking back
Anecdotal = stories or narratives

The medical-scientific community has established a strict hierarchy to judge the value of three different kinds of clinical data to support a mode of therapy.

(1) **The randomized prospective clinical trial** is judged the most important scientific evidence to support clinical treatment. This kind of trial, which is planned in advance, tests the efficacy of a particular therapy. For example, in the United States, to test the efficacy of two different kinds of therapy for early breast cancer, a large clinical trial was performed that prospectively and randomly allocated patients to be treated either by (a) a mastectomy, or (b) excision of the tumor only, leaving the breast preserved, followed by radiation therapy. This trial demonstrated equivalent survival rates for both treatments. The medical community has universally accepted this trial as strong *scientific evidence* that breast

see PROSPECTIVE—cont. page 2



NAMI-CAN

copy

expressly for *Children and Adolescents*

National Alliance for the Mentally Ill Children and Adolescents Network,
an affiliate of NAMI, with over 130,000 members nationwide

+++++

MAILING ADDRESS:

NAMI CAN NEWS

8 Country Club Drive

Woodbridge, Connecticut 06525

PHONE: (203)-397-9269

February 25, 1991

Frederick Goodwin, M.D., Administrator
Department of Health & Human Services--Parklawn Building 12-C-06
5600 Fishers Lane
Alcohol, Drug Abuse and "Mental Health" Administration
Rockville, Maryland 20857

Dear Dr. Goodwin:

I want to applaud the direction at ADAMHA and the NIMH that has established CASSP under a new leadership that will seek to scientifically evaluate services to the severely mentally ill. It is absolutely essential to establish treatment and services on based on science, evidence and efficacy, instead of on mere theory, opinion and belief.

I am writing to comment on the recent National Mental Health Association's (NMHA) statement and recommendation about CASSP, which apparently has been endorsed by some other "mental health" organizations (Federation of Families for Children's Mental Health, National Association of State Mental Health Program Directors, National Association of State Mental Health Representatives for Children and Youth). Please note that these organizations are all concerned with "mental health" issues. Please note also that *the one organization devoted solely to the needs of the most severely ill people who have the neurobiological diseases/disorders called "mental" illness* has **not** endorsed the NMHA statement and recommendations about CASSP.

It is important to note that the NMHA statement and recommendations about CASSP uses antiquated language that lumps together under the non-scientific rubric of "severely emotionally disturbed" (SED) children and adolescents who have (a) biologically-caused illnesses (the biologically-based brain diseases--**BBBD**--called "mental" illness, including, for example, schizophrenia, bipolar and unipolar disorders, autism, pervasive developmental disorder, obsessive-compulsive disorder, Tourette's disorder, anxiety and panic disorders, attention deficit

NATIONAL ALLIANCE FOR THE MENTALLY ILL

2101 WILSON BOULEVARD, SUITE 302 • ARLINGTON, VA 22201
703-524-7600 • FAX 703-524-9094

disorder, hyperactivity, attention deficit hyperactivity disorder) with (b) sociologically- or environmentally-caused "mental health" problems (e.g. abuse, neglect, crime, poverty; neurotic, emotional, psychological, or life-adjustment issues).

In light of the past 10 years of neuroscience and basic science research--a good amount of which you yourself have done and/or sponsored at the NIMH--it is scientifically unacceptable to continue to lump together people with biologically-caused disorders (BBBD) and people with sociologically- or environmentally-caused "mental health" (i.e. psychological) problems.

In fact, both groups of severely disabled children (those with a BBBD, and those with serious "mental health" problems) need--and deserve to have--treatments and services *geared to their specific disabilities, based on the etiology of those disabilities.*

Therefore, I strongly urge the NIMH to:

- (1) continue its scientific investigation of CASSP proposals and projects.

- (2) reword its definition of CASSP obligations. The new language must state specifically that children suffering from the neurobiological diseases/disorders named above must be recognized as a different category from children with "mental health" problems. Children with a BBBD are entitled to treatment and services geared to their *biologically-based* disorders.

It is a disgrace that federally-funded programs continue to abuse people severely and chronically ill with neurobiological disorders by calling those devastating brain diseases by the non-scientific terms of "mental health" problems or "emotional disturbance."

For the child, adolescent, or adult who has a serious chronic neurobiological disorder--and for such a person's caring family--the terms "mental health" and "emotional disturbance" are obnoxious and offensive terms, a vestige of psychoanalytical denial of the reality of these brain diseases. A person with a BBBD has a serious, chronic brain disease. If someone has a brain tumor or any other kind of cancer, no one speaks about "**tumor health.**" Therefore, it is unacceptable to speak about "**mental health**" for a person with a BBBD. In addition, we must remove the stigma from BBBD so that people can talk openly without fear and guilt about these diseases. Also, the phrase "emotional disturbance" implies that the person has a psychological or "mental health" problem, not a biological disease. Only if you are speaking about malfunction and/or malformation of the limbic system of the brain would it be acceptable to speak about "emotional disturbance" for a person seriously ill with a BBBD.

I am not suggesting that the CASSP mandate discard the words "mental health" or "emotional disturbance." Those words may be appropriate for the "mental health" problems named above. I am, however, strongly urging that the CASSP mandate *specifically include in its wording the need to devise, support, and foster appropriate services for children and adolescents afflicted with the neurobiological diseases/disorders named above, and appropriate supportive help, including*

respite care, for their caring families.

This is the **DECADE OF THE BRAIN**. What better time than now to acknowledge the need to address in appropriate language and services, all children, adolescents and adults severely handicapped by these devastating neurobiological diseases?

With appreciation for your interest in these scientific and human matters, and with best wishes,

Sincerely,



Enid Peschel, Ph.D.
Editor, **NAMI CAN NEWS**;
Co-Director, Program for Humanities in
Medicine
Assistant Professor (Adjunct), Department of
Internal Medicine
Yale University School of Medicine

cc: D. Allan Bromley, Ph.D. Science Advisor to President Bush
Alan Leshner, Acting Director, NIMH
Laurie Flynn, Executive Director, NAMI

"CORRESPONDENCE TRACKING"

TYPE: Action Item

DOCUMENT NUMBER: 9120601

FROM: GENEL, Myron; Yale University

TO: DAB

DATE OF
CORRESPONDENCE: 02/25/91

SUBJECT: Enclosing final report of AAMC Task Force,
"Supplying Physicians for Future Needs"

ASSIGNED TO: D.A. Henderson

ACTION REQUIRED: Comments to DAB

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED: 03/11/91

COPIES TO: Rachel Levinson

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 03/04/91
DATE RECEIVED DLS: 03/06/91

FILE: 
7 - Life Sciences * EDUCATION

Yale University

February 25, 1991

D. Allan Bromley, Ph.D.

Assistant to the President for Science & Technology
Director, Office of Science & Technology Policy
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Washington, DC 20506

Office of Government and Community Affairs

School of Medicine

Sterling Hall of Medicine

333 Cedar Street

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Myron Genel, M.D.

Associate Dean

Campus address:

1202 SHM

333 Cedar Street

Telephone:

203 785-6019

FAX:

203 785-7208

Dear Allan:

Per our conversation last Wednesday en route, circuitously, to National Airport, I am enclosing a copy of the final report from the AAMC Task Force on Physician Supply entitled "Supplying Physicians for Future Needs". The report, which was released last fall, is the product of almost four years of research and deliberations within the Task Force Steering Committee and its four subcommittees and reflects considerable discussion of the task force interim conclusions with the Association's membership and governance.

I call your attention to Part I of the report, which provides an excellent historical and statistical background as well as an executive summary of the task force conclusions. Particularly relevant to our discussion Wednesday and for the upcoming spring meeting of the Council of Academic Societies next month in Savannah is Part IV, the 35 page report of the Subcommittee on Implications of Physician Supply Issues on Programs for the Education of Biomedical Scientists, chaired by David Korn, Vice President and Dean of the Stanford Medical School. The subcommittee's conclusions and recommendations begin on page 26 of this section and should be of interest to you and your staff.

I anticipate that many of these themes will be elaborated upon in Savannah March 25-27 during the spring meeting of the Council of Academic Societies built around the theme "Recruiting and Nurturing Young Faculty and Investigators". I look forward to your keynote address Monday evening, expecting that it will provide a provocative prologue for our discussions and hope that you can remain with us for a portion of the meeting which follows. I certainly hope that your travel arrangements will prove more successful than those we experienced from Bridgeport last week.

With best regards,


Myron Genel, M.D.
Professor of Pediatrics
Associate Dean
Chairman, Council of Academic Societies, AAMC

MG:pac

cc: Robert G. Petersdorf, M.D., President, AAMC

Thomas E. Malone, Ph.D., Vice President for Biomedical Research, AAMC

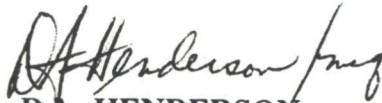
Enclosure

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

March 11, 1991

MEMORANDUM FOR D. ALLAN BROMLEY

FROM:


D.A. HENDERSON

SUBJECT:

COMMENTS ON AAMC REPORT

I have read the AAMC Report (sent to you by Myron Genel at Yale) on "Supplying Physicians for Future Needs" chaired by Dan Tosteson. It is basically descriptive and offers no new and illuminating insights nor any policy options which are controversial or seriously address problems.

As preface to the piece on research, it points out that there are now 597,000 physicians; by 2000, there will be 708,600 (an increase from 239/100,000 to 264/100,000). It is estimated (per the report) that each added physician increases the annual cost of health care by \$800,000 per annum. The Committee concludes that because it cannot document that unnecessary procedures are being done, it "does not conclude there is an impending surplus" whatever other bodies may believe. From the tenor of the report, however, it is clear that there is great unease.

Applicants to medical schools fell sharply from 42,000 in 1975 to 29,000 in 1990 but the number appears to be stabilizing. Matriculants, however, remained essentially constant over the past decade at about 17,000. Numbers of faculty increased from 50,000 in 1980 to 70,000 in 1988. Almost all growth is in the chemical sciences.

Most medical specialties are deemed to be in balance or in surplus (most surgical specialties). There are a few shortage areas -- e.g., psychiatry, preventive medicine, and emergency medicine -- and there is a belief that many more primary care physicians should be trained. Nevertheless, the proportion of physicians trained in primary care decreased by almost half between 1981 and 1989. All schools are enjoined to do better.

David Korn's Committee on Programs for the Education of Biomedical Scientists, to which your attention is drawn, stresses the importance of academic medical centers as the principal focus for biomedical research and for Ph.D. training and emphasizes their role in advancing the profession during a time of exponential growth in knowledge. It is noted that this research effort is concentrated with 40 of 127 schools receiving 72% of all Federal research support. The growth of Federal support is noted in pointing out that the National Institutes of Health (NIH) budget grew more than 250-fold (in constant dollars) between 1945 and 1990; and grew in current dollars from about \$3.5 billion in 1982 to \$7.5 billion in 1989.

The Committee highlights reasons for the current stress:

1. Attenuation in the rate of increase in Federal funding coincides with a sharp upturn in demand resulting from the excitement generated by the new biology. It is noted that industrial support has been "sporadic, limited to narrowly focused projects, and circumscribed by high proprietary protections with relatively little funding for broad basic research." It was hoped this might change.
2. Obsolete facilities, equipment and instrumentation result from a 20-year Federal aversion to financing construction, renovation, etc. Notably, such funds as have been made available (\$270 million in FY '88 and \$203 million in FY '89) are almost all earmarked by Congressional committees.
3. Training programs have diminished in number and stipend levels have decreased. Training as a percentage of NIH's budget decreased from about 5% (1977-1981) to 3.5-4.0% (1984 to present) and training positions decreased from 13,000 in FY '71 to about 10,500 today. Diminishing numbers of physicians in post-doctoral research positions became apparent in 1975 but is beginning to rise today.

The Committee concludes by noting that research investments to date have been highly productive but that the accomplishments need to be better understood by the public especially at a time when the national economy is experiencing limited growth. The view is expressed that it is timely to explore the Federal government's commitment to its role as principal patron of basic science and the vitality of its relationship with academe. Also pointed out is the need to maintain a continuing infusion of fresh scientific talent, to sustain and expand the effort.

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION

DOCUMENT NUMBER: 9120725

FROM: SCHAMBRA, Philip E.: FOGARTY INTERNATIONAL CENTER, NIH

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 02/14/91

SUBJECT: RESULTS OF NIH DISCUSSIONS WITH USSR ACADEMY OF
SCIENCES.

ASSIGNED TO:

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO: D. Allan Bromley
Life Sciences
Thomas Ratchford

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 03/12/91

FILE: INTERNATIONAL***LIFE SCIENCES**

-USSR



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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National Institutes of Health
Bethesda, Maryland 20892

31 MAR 12 P 2:32

February 14, 1991

OFFICE OF THE
DIRECTOR

TO: Dr. D. Allan Bromley
Director
Office of Science and Technology Policy
Executive Office of the President
Through: Acting Director, NIH *W. A. Raulo*
Assistant Secretary for Health *James O. Mason*
MAR 7 1991

FROM: Director, Fogarty International Center, NIH

SUBJECT: Results of NIH Discussions with USSR Academy of Sciences

At the First Joint Commission Meeting under the US-USSR Basic Sciences Agreement, during which I represented the Public Health Service at Dr. Mason's request, it was agreed that NIH and the Soviet Academy of Sciences would explore the possibility of cooperation in basic biological science. We have just completed a highly successful series of meetings at NIH with a delegation from the Academy. The Summary of Discussions is attached for your information.

Over the next several months, we will further explore the option of an Agreement with the Academy of Sciences during reciprocal visits to Academy institutes by NIH scientific leaders. In the meantime, direct scientist-to-scientist cooperation will continue utilizing existing mechanisms at NIH and the Academy.

We will keep you informed of further developments.

Philip E. Schambra
Philip E. Schambra, Ph.D.

Attachment

SUMMARY OF DISCUSSIONS
BETWEEN
THE USSR ACADEMY OF SCIENCES
AND
THE NATIONAL INSTITUTES OF HEALTH

January 31-February 8, 1991
Bethesda, Maryland

In accordance with the agreement reached at the First Joint Commission Meeting under the US-USSR Agreement on Cooperation in the Field of Basic Scientific Research, a delegation from the Academy of Sciences of the USSR (ASUSSR) visited the National Institutes of Health (NIH) January 31-February 8, 1991 to explore cooperation in basic biomedical science. The Soviet delegation was led by Academician Rem V. Petrov, Vice President, ASUSSR. The schedule of meetings and list of participants are attached as Annex I and Annex II.

During their visit, the delegation met with the Acting Director, NIH; the Director of the Fogarty International Center; and directors and staff of the National Cancer Institute; the National Institute of Child Health and Human Development; the National Institute of Allergy and Infectious Diseases; the National Eye Institute; the National Institute of Neurological Disorders and Stroke; the National Institute of Diabetes and Digestive and Kidney Diseases; the National Library of Medicine; the National Center for Human Genome Research; the Warren G. Magnuson Clinical Center; and the Office of AIDS Research. Academicians Petrov and Igor M. Makarov also participated in the meeting of the Fogarty International Center's Advisory Board on February 5.

Among the topics discussed for possible cooperation were cancer, immunology and AIDS, molecular biology and genetics, neurobiology, clinical research and scientific information exchange. Specific research projects in these areas were also discussed.

Both sides agreed that the basic principle of cooperation should be the promotion of direct contacts between scientists, who would bear the primary responsibility for developing specific collaborative research activities.

Both sides discussed the mechanisms to support cooperation that currently exist at NIH and the ASUSSR. For NIH, these include research grants, the Visiting Program and Guest Researcher Program for foreign scientists, the Senior International Fellowship Program for U.S. scientists, the International AIDS Epidemiology Training and Research Grants Program, and a special Fogarty Center fund to promote cooperation between NIH scientists and Soviet scientists. In addition, the ASUSSR was

invited to participate in the International Research Fellowship Program for foreign postdoctoral scientists to conduct research in the U.S. The ASUSSR will explore the establishment of a Soviet nominating committee under this program to enable Soviet scientists to compete for these awards. It was also agreed to explore the possibility of extending the US-USSR Health Scientist Exchange Program, which is currently supported by the USSR Ministry of Health and the Fogarty International Center, to the ASUSSR. The ASUSSR can provide housing facilities for short- and long-term visiting scientists and salary support for extended stays.

Both sides agreed that it would be useful to meet again in the USSR prior to the second Joint Commission meeting under the US-USSR Basic Sciences Agreement, tentatively in late April or early May, 1991.



William F. Raub
Acting Director
National Institutes of Health



Rem V. Petrov
Vice President
USSR Academy of Sciences



Philip E. Schambra
Director
Fogarty International Center
National Institutes of Health



Igor M. Makarov
Chief Scientific Secretary
USSR Academy of Sciences

Signed in Bethesda, Maryland, February 8, 1991

ANNEX I

SCHEDULE OF MEETINGS
VISIT OF THE DELEGATION FROM THE
U.S.S.R. ACADEMY OF SCIENCE

Thursday, January 31, 1991

- 10:30 Dr. Shiyan meets with Dr. Philip E. Schambra, Director,
Fogarty International Center. NIH, Building 31, Room
B2C39 Tel: 496-1415
- 12:00 Lunch with Ms. Alexandra Stepanian and Mr. F. Gray
Handley, NIH.

Friday, February 1, 1991

- 9:00 Acad. Georgiev meets with Dr. Gary Felsenfeld, National
Institute of Diabetes and Digestive and Kidney
Diseases, Building 2, Room 301
- 11:00 Acad. Georgiev and Dr. Shiyan meet with Dr. Duane
Alexander, Director, National Institute of Child
Health and Human Development, NIH, Building 31, Room
2A04 Tel: 496-3454
- 3:00 Acad. Georgiev gives a lecture at the National
Institute of Diabetes and Digestive and Kidney
Diseases, Building 2, Room 102

Saturday, February 2, 1991

Day free

Sunday, February 3, 1991

Arrival of Academicians Petrov and Makarov

Day free

Monday, February 4, 1991

- 9:30 Acads. Petrov, Makarov, Georgiev and Dr. Shiyan meet with Dr. William F. Raub, Acting Director, NIH, Building 1, Room 114 Tel: 496-2121
- 10:00 Acads. Petrov, Makarov, Georgiev and Dr. Shiyan meet with Dr. Jack Whitescarver, Deputy Director, Office of AIDS research, Dr. Karl Western, NIAID, and Ms. Linda Reck, Office of AIDS research. Building 1, Room 201. Tel: 496-0357
- Lunch Free
- 1:00 Acads. Petrov, Makarov, Dr. Shiyan have meetings at the National Academy of Sciences, 2101 Constitution Avenue, N.W.

Tuesday, February 5, 1991

Academician Georgiev goes to Baltimore for meetings.

- 10:45 Acads. Petrov, Makarov, Dr. Shiyan attend Fogarty International Center Advisory Board Meeting. Presentations by Academicians Petrov and Makarov. NIH, Stone House
- 12 noon Advisory Board Lunch at Stone House
- 3:30 Acads. Petrov, Makarov and Dr. Shiyan visit the National Science Foundation.

Arrival of Acads. Simonov and Ivanov, and Profs. Zakharov and Karaulov.

Wednesday, February 6, 1991

- 11:00 Full delegation meets with Dr. Philip E. Schambra at Stone House.
- 12 noon Formal lunch hosted by Dr. William F. Raub, Acting Director, NIH, at Stone House.

- 1:30 Full delegation meets with Dr. Samuel Broder, Director, National Cancer Institute, Conference Room, Stone House.
- 2:30 Delegation meets with Dr. Kenneth Bridbord, Chief, International Studies Branch, Fogarty International Center.
- 2:30 Academician Ivanov meets with Dr. Jay Berzofsky, National Cancer Institute, Building 10, Room 6B06. Tel: 496-6874
- 4:00 Full delegation meets with Dr. John Gallin, Scientific Director NIAID, and NIAID intramural staff. Stone House.

Thursday, February 7th, 1991

- 9:00 Acads. Petrov and Ivanov meet with Dr. Robert Nussenblatt, National Eye Institute, Building 10, Room 10N202. Tel: 496-3123
- 10:30 Academicians Petrov, Simonov, Profs. Zakharov and Karaulov visit NIH Clinical Center. Ms. Hilda Mejia will escort to meetings.
- 11:00 Academician Ivanov meets with Dr. Peng Loh, National Institute of Child Health and Human Development, Building 36, Room 4A21. Tel: 496-3239.
- 1:00 Delegation meets with National Institute of Allergy and Infectious Diseases Extramural Division Staff, NIH, Building 31, Room 7A03.
- 3:00 Delegation meets with Dr. Murray Goldstein, Director, National Institute of Neurological Disorders and Stroke, Building 31, Room 8A52. Tel: 496-9746.
- 5:00 Academician Ivanov meets with Dr. Harold Gainer, Chief, Laboratory of Neurochemistry, National Institute of Neurological Disorders and Stroke, Building 36, Room 5A05.

Friday, February 8, 1991

- 10:30 Delegation meets with Mr. Kent A. Smith, Deputy Director, National Library of Medicine, Building 38, Room 2E17B. Tel: 496-6661. Tour of the National Library of Medicine, Dr. Richard Hsieh, Assistant Director for International Programs, National Library of Medicine.

- 1:00 Acads. Petrov and Ivanov meet with Dr. Carl Kupfer,
Director, National Eye Institute, and Dr. Robert
Nussenblatt, Clinical Director, National Eye Institute,
NIH, Building 31, Room 6A03. Tel: 496-2234
- 4:00 Delegation meets with Dr. Philip E. Schambra at Stone
House, NIH. Concluding discussions.
- 5:30 Reception at Stone House

Monday, February 11, 1991

Professor Karaulov spends February 11th and 12th with Dr. Albert
Saah at Johns Hopkins University.

Tuesday, Wednesday, Thursday, February 13, 14, 15

Professor Karaulov attends Multicenter AIDS Cohort Study Meeting
at Sheraton Potomac Hotel in Rockville, Maryland.

ANNEX II

LIST OF PARTICIPANTS

USSR Delegation

Academician R. V. Petrov
Vice President, ASUSSR

Academician I. M. Makarov
Chief Scientific Secretary, ASUSSR

Academician P.V. Simonov
Academician-Secretary
Department of Physiology, ASUSSR

Academician V.T. Ivanov
Director
Shemyakin Institute of Bioorganic Chemistry, ASUSSR

Academician G.P. Georgiev
Director
Institute of Gene Biology, ASUSSR

Professor V.N. Zakharov
Director
Office of Medical Affairs, ASUSSR

Professor A.V. Karaulov
Director
Institute of Biomedical Research and Therapy
USSR Ministry of Health

Dr. Yu K. Shiyan
Inspector
Presidium, ASUSSR

Dr. A. V. Shishkin
Counselor
Embassy of the USSR

Dr. A.A. Sokhin
Counselor (Medicine)
Embassy of the USSR

NIH Participants

Dr. William F. Raub
Acting Director, NIH

Fogarty International Center

Dr. Philip E. Schambra
Director

Dr. Kenneth Bridbord
Chief
International Studies Branch

Mr. F. Gray Handley
Chief
International Coordination and Liaison Branch

Ms. Alexandra Stepanian
Program Officer for the Soviet Union
International Coordination and Liaison Branch

National Cancer Institute

Dr. Samuel Broder
Director

Dr. Jay Berzofsky
Metabolism Branch
Division of Cancer Biology, Diagnosis, and Centers

Dr. Federico Welsch
Associate Director for International Affairs

National Institute of Allergy and Infectious Diseases

Dr. James C. Hill
Deputy Director

Dr. John Gallin
Scientific Director

Dr. Robert M. Chanock
Chief
Laboratory of Immunology

Dr. William E. Paul
Chief
Laboratory of Immunology

Dr. Ronald E. Schwartz
Chief
Laboratory of Cellular and Molecular Immunology

Dr. Scott Koenig
Laboratory of Immunoregulation

Dr. Robert Purcell
Laboratory of Clinical Investigation

Dr. Michael Sitkovsky
Laboratory of Immunology

Dr. Warren Strober
Laboratory of Clinical Investigation

Dr. Robert Goldstein
Director
Division of Allergy, Immunology and Transplantation (DAIT)

Dr. Suzana Serrate-Stein
Autoimmunity, Clinical Immunology Branch, DAIT

Dr. Stephen M. Rose
Chief
Genetics and Transplantation Branch, DAIT

Dr. George Curlin
Deputy Director
Division of Microbiology and Infectious Diseases (DMID)

Dr. Jane Kinsel
Special Assistant, DMID

Dr. Leslye Johnson
Chief
Enteric Diseases Branch, DMID

Dr. Pamel McInnes
Bacterial Diseases, Respiratory Diseases Branch, DMID

Dr. John McGowan
Associate Director, Basic Research and Development Program
Division of AIDS (DAIDS)

Dr. Robert Fischer
Epidemiology Branch, DAIDS

Dr. Karl Western
Assistant Director for International Research

Dr. Kathryn Aultman
International Health Program Officer

National Institute of Child Health and Human Development

Dr. Duane Alexander
Director

Dr. Igor Dawid
Chief
Laboratory of Molecular Genetics

Mr. James G. Hill
Chief
Office of Science Policy and Analysis

Dr. Bruce Howard
Laboratory Chief

Dr. Peng Loh
Section Chief
Laboratory of Cellular Neurobiology

Dr. Heiner Westphal
Chief
Laboratory of Mammalian Genes and Development

Dr. Alan Wolffe
Laboratory Chief

National Institute of Diabetes and Digestive and Kidney
Diseases

Dr. Gary Felsenfeld
Laboratory of Molecular Biology

Dr. Alan Schechter
Chief, Laboratory of Chemical Biology

National Eye Institute

Dr. Carl Kupfer
Director

Dr. Robert Nussenblatt
Clinical Director

National Heart, Lung, and Blood Institute

Dr. David Goldstein
Hypertension-Endocrine Branch

National Institute of Neurological Disorders and Stroke

Dr. Murray Goldstein
Director

Dr. Roger Porter
Deputy Director

Dr. Harold Gainer
Laboratory of Neurochemistry
Division of Intramural Research

Dr. Novera Spector
Division of Fundamental Neurosciences

National Library of Medicine

Mr. Kent Smith
Deputy Director

Dr. Harold Schoolman
Deputy Director for Research and Education

Dr. Richard Hsieh
Assistant Director for International Programs

National Center for Human Genome Research

Dr. Elke Jordan
Deputy Director

Office of AIDS Research

Dr. Jack Whitescarver
Deputy Director

Ms. Linda Reck
Program Analyst

Withdrawal/Redaction Sheet

(George Bush Library)

Document No. and Type	Subject/Title of Document	Date	Restriction	Class.
01. Letter	To: Allan Bromley From: Norman Rabin Re: Complaint [personal information redacted] (1 pp.)	2/12/91	(b)(6)	

Collection:

Record Group: Bush Presidential Records
Office: Science and Technology Policy, Office of (OSTP)
Series: Bromley, D. Allan, Files
Subseries: General Science Files
WHORM Cat.:
File Location: Life Sciences: General [3 of 4] [1991]

Date Closed:	3/15/2010	OA/ID Number:	62038-003
FOIA/SYS Case #:	2005-0336-F	Appeal Case #:	
Re-review Case #:		Appeal Disposition:	
P-2/P-5 Review Case #:		Disposition Date:	
AR Case #:		MR Case #:	
AR Disposition:		MR Disposition:	
AR Disposition Date:		MR Disposition Date:	

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

Freedom of Information Act - [5 U.S.C. 552(b)]

P-1 National Security Classified Information [(a)(1) of the PRA]
P-2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P-3 Release would violate a Federal statute [(a)(3) of the PRA]
P-4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P-5 Release would disclose confidential advice between the President and his advisors, or between such advisors [(a)(5) of the PRA]
P-6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.

PRM. Removed as a personal record misfile.

(b)(1) National security classified information [(b)(1) of the FOIA]
(b)(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
(b)(3) Release would violate a Federal statute [(b)(3) of the FOIA]
(b)(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
(b)(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
(b)(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
(b)(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
(b)(9) Release would disclose geological or geophysical information

"CORRESPONDENCE TRACKING"

TYPE: Action Item

DOCUMENT NUMBER: 9120372

FROM: SIMPSON, George; Am Coll of Neuropsychopharmacology, Phil PA

TO: DAB

DATE OF
CORRESPONDENCE: 02/07/91

SUBJECT: Request for meeting on March 11 or 12

ASSIGNED TO: D.A. Henderson

ACTION REQUIRED: Response

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO:

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS: Bromley wrote on his copy and asked if DAB wanted to see the group. It conflicts, however, with the PAHO meeting in Guatemala.

DATE RECEIVED: 02/12/91
DATE RECEIVED DLS: 02/13/91

FILE: DLS

P- Life Sciences

**EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506**

February 14, 1991

NOTE TO ALLAN BROMLEY

FROM: D.A. HENDERSON

**RE: REQUEST FOR MEETING ON MARCH 11 OR 12
FROM GEORGE SIMPSON (AMERICAN
COLLEGE OF NEUROPSYCHOPHARMACOLOGY**

I will be Guatemala that week at a PAHO meeting. This group is dealing with a fascinating array of new developments in an important field but it is a small group and hardly necessary for you to see for a courtesy visit.

"CORRESPONDENCE TRACKING"

TYPE: ACTION

DOCUMENT NUMBER: 9120372

FROM: SIMPSON, GEORGE M. (AMERICAN COLLEGE OF
NEUROPSYCHOPHARMACOLOGY)

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 02/07/91

SUBJECT: REQUEST FOR A MEETING EITHER MARCH 11 OR 12

ASSIGNED TO: Life Sciences

ACTION REQUIRED:

SENDER'S DUE DATE:

OSTP DUE DATE:

DATE COMPLETED:

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 02/12/91

FILE: LIFE SCIENCES

9120372



RECEIVED
American College of Neuropsychopharmacology

91 FEB 12 AIO: 23

OFFICE OF THE DIRECTOR
February 7, 1991

Honorable D. Allan Bromley
Assistant to the President for
Science and Technology and Director,
Office of Science and Technology Policy
Room 360
Old Executive Office Building
Washington, D.C. 20506

Dear Dr. Bromley:

As President of the American College of Neuropsychopharmacology ("ACNP"), I request the honor of meeting with you during the ACNP Council's Spring Meeting in Washington, D.C. The governing body of the ACNP, its seven member Council and four officers will be in Washington, D.C. on March 10-12, 1990. We would appreciate the opportunity to meet at your convenience either on March 11 or 12 in your office to discuss several issues of immediate concern to our national membership. We will furnish you with a list of attendees and a brief outline of proposed topics following confirmation of a meeting date.

The ACNP is an interdisciplinary association of nationally known and respected scientists throughout America. Our members are actively engaged in research concerning the relationship of the central nervous systems to causes and treatment of drug abuse, alcoholism, and mental illness. We share your interest in a broad range of scientific issues of current significance including research funding, development of neuropsychopharmacologic drugs, animal research and scientific misconduct.

We will be meeting with top Administration health policymakers, Members of Congress and staff during our visit. You have been kind enough to meet with us in the past. We look forward to updating you concerning the current status of our biomedical research and several legislative and health policy issues of importance to our membership.

OFFICE OF THE PRESIDENT George M. Simons, M.D. Medical College of PA/EPI Department of Psychiatry 3200 Henry Avenue Philadelphia, PA 19129	PRESIDENT-ELECT Irwin Kopin, M.D. PAST PRESIDENT Richard I. Shader, M.D.	SECRETARY Oakley Ray, Ph.D. TREASURER David M. Engelhardt, M.D.	COUNCIL Roger E. Meyer, M.D. (89-91) Dennis L. Murphy, M.D. (89-91) Thomas J. Detre, M.D. (90-92) John M. Kane (90-92) Saul Schanberg, M.D., Ph.D. (91-93) Donald S. Robinson, M.D. (91-93)
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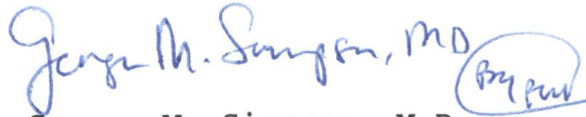
- 2 -

In our most recent meeting with Secretary Sullivan, at our conference in December, he suggested we should meet with you on our next visit to Washington.

Thank you for your consideration of this request. We look forward to your response. Our Washington, D.C. legislative counsel, Paul L. Perito, Marc J. Scheineson or I will contact your office shortly to schedule a convenient time to meet.

Best regards.

Respectfully,


George M. Simpson, M.D.
President

cc: Paul L. Perito, Esq.
Marc J. Scheineson, Esq.

"CORRESPONDENCE TRACKING"

TYPE: Action Item

DOCUMENT NUMBER: 9120277

FROM: ROPER, William; CDC, Atlanta, GA

TO: DAB

DATE OF
CORRESPONDENCE: 02/01/91

SUBJECT: Invitation to DAB or any staff to attend meeting to
review the risks of human immunodeficiency virus and
hepatitis B virus transmission to patients during
invasive medical and dental procedures.

ASSIGNED TO: D.A. Henderson

ACTION REQUIRED: None

SENDER'S DUE DATE: 02/13/91

OSTP DUE DATE: 02/11/91

DATE COMPLETED: 02/12/91

COPIES TO: Rachel Levinson
Alicia Dustira

WHITE HOUSE TRACKING #:

CONTACT PERSON: Jacquelyn Polder

REMARKS:

DATE RECEIVED: 02/04/91
DATE RECEIVED DLS: 02/07/91

FILE: DLS-AIDS

P- Life Sciences

891A-210

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

February 12, 1991

Dear Bill,

Regrettably, no one from the Office of Science and Technology Policy is available to attend the February 21-22 meeting in estimating risks of HIV transmission. I personally have studied the document with some care and find myself deeply concerned with the methodology and interpretations. I would hope that the meeting serves well to address the issues involved. Please arrange to inform me as to the outcome, if you would.

I was sorry to have to miss one meeting. I look forward, however, to keeping in close touch with my alma mater. Do feel free to call if I can be of help.

All best regards,



D.A. Henderson, M.D., M.P.H.
Consultant

William L. Roper, M.D., M.P.H.
Director
Centers for Disease Control
Atlanta, Georgia 30333



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

RECEIVED

Centers for Disease Control
Atlanta GA 30333

91 FEB 4 P 5:19 FEB 01 1991

The Honorable D. Allan Bromley, Ph.D.
Assistant to the President for
Science and Technology
Old Executive Office Building
17th Street and Pennsylvania Avenue, NW
Washington, D.C. 20506

OFFICE OF THE
DIRECTOR

Dear Dr. Bromley:

On February 21-22, 1991, the Centers for Disease Control (CDC) will convene a meeting to review the risks of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) transmission to patients during invasive medical and dental procedures. This meeting will allow representatives of various groups and organizations and members of the public to review and comment on available risk assessment data and the implications of these risks.

Attached you will find the material being sent to parties interested in this issue. Included is a copy of the *Federal Register* notice that gives specific information on the meeting and the procedures to follow for persons interested in commenting.

The meeting will be held in Atlanta, Georgia, at the Hyatt Regency Hotel (downtown), 265 Peachtree Street, N.E., from 8:30 a.m. on Thursday, February 21, through 4:00 p.m. on Friday, February 22.

If you or your staff are interested in attending or obtaining additional information, please contact Jacquelyn Polder, B.S.N., M.P.H., or David Bell, M.D., of CDC's Hospital Infections Program (404-639-1644) by February 13, 1991.

CDC looks forward to obtaining advice on this complex issue and welcomes your participation in this important effort.

Sincerely,

William L. Roper, M.D., M.P.H.
Director

Enclosure

Dated: January 11, 1991.

Fred L. Sims,

*Deputy Assistant Commissioner for
Information Resources Management Policy.*

[FR Doc. 91-1455 Filed 1-22-91; 8:45 am]

BILLING CODE 6820-25-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control

Open Meeting on the Risks of Transmission of Bloodborne Pathogens to Patients During Invasive Procedures

ACTION: Notice of public meeting.

SUMMARY: The Centers for Disease Control (CDC) will convene a meeting to review the risks of HIV and hepatitis B virus (HBV) transmission to patients during certain invasive medical and dental procedures. This meeting will allow representatives of various groups and organizations and members of the public to review and comment on available risk assessment data and the implications of these risks. Background data will be provided upon request prior to the meeting.

TIME AND DATES: The 2-day meeting will begin at 8:30 a.m. on Thursday, February 21, 1991, and will conclude at 4 p.m. on Friday, February 22, 1991.

Persons interested in making oral comments at the meeting should provide written notification, as specified below, for receipt by the meeting organizer, PACE Enterprises, no later than close of business on Wednesday, February 13, 1991.

Persons wishing to provide written comments for the record may do so at any time, as long as such written comments are received by the meeting organizer, PACE Enterprise, by close of business on Friday, March 22, 1991.

MEETING LOCATION: Hyatt Regency Hotel, 265 Peachtree Street, NE., Atlanta, Georgia 30303, telephone 404/577-1234.

STATUS: Open to the public, limited only by the space available. The meeting room will accommodate 1,000.

FOR FURTHER INFORMATION CONTACT: PACE Enterprises, 17 Executive Park Drive, suite 200, Atlanta, Georgia 30329, telephone 404/633-8610.

SUPPLEMENTARY INFORMATION:

A. In General: The purpose of this meeting is (1) to review the risks of HIV and HBV transmission to patients during certain invasive medical and dental procedures, and (2) to allow representatives of various groups and organizations and members of the public

to review and comment on available risk assessment data and on the implications of these risks.

The first day of the meeting is scheduled to consist of presentations of risk assessment data by CDC and presentations from invited speakers that represent various viewpoints concerning the implications of the data available.

The second day of the meeting will provide an opportunity for representatives of groups and organizations and members of the public to comment on the risk assessment data, the implications of these risks, and the previous day's presentations.

Persons interested in attending the meeting and/or obtaining an updated agenda, background data, and additional information should contact the CDC meeting organizer, PACE Enterprises, 17 Executive Park Drive, Suite 200, Atlanta, Georgia 30329, telephone 404/633-8610.

B. Oral Comments: Persons interested in providing oral comments at the meeting should notify the meeting organizer, PACE Enterprises, at the above address in writing. Such written request must be received by the meeting organizer no later than close of business Wednesday, February 13, 1991.

All requests for making oral comments at the meeting should contain the name, address, telephone number, and any organizational affiliation of the person desiring to give oral comments.

Depending upon the time available and the number of requests to present oral comments, it may be necessary to restrict the length of time for each commenter. Accordingly, CDC may request that oral comments be limited to five minutes.

Requesters will be notified by mail or telephone of the length of time available to the person and the approximate time on the agenda when the person's comments are scheduled to begin.

If a person is not present when his or her comments are scheduled to begin, the remaining commenters will be heard in order. At the conclusion, an attempt will be made to hear any scheduled commenters who missed their assigned time. Interested persons who did not request an opportunity in advance to provide oral comments may be given an opportunity to do so, at the discretion of the presiding officer.

C. Written Comments: Anyone wishing to submit written comments concerning the available risk assessment data, the implications of these risks, or the oral presentations made at the public meeting should provide such written comments to PACE Enterprises, 17 Executive Park Drive,

suite 200, Atlanta, Georgia 30329, telephone 404/633-8610.

Such written comments must be received by the meeting organizer, PACE Enterprises, no later than close of business Friday, March 22, 1991.

D. Transcript: The proceedings of this meeting will be transcribed. Any interested person may, consistent with the orderly conduct of the meeting, record or otherwise make a transcript of the meeting.

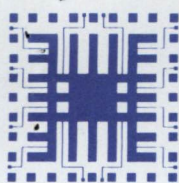
Dated: January 17, 1991.

Elvin Hilmyer,

*Associate Director for Policy Coordination,
Centers for Disease Control.*

[FR Doc. 91-1602 Filed 1-18-91; 10:59 am]

BILLING CODE 4160-18-M



PACE ENTERPRISES

NOTE TO PARTICIPANTS

PACE Enterprises, Inc. is pleased to serve as Conference Coordinator for the Meeting on Risk of Transmission of Bloodborne Pathogens to Patients during Invasive Procedures. This meeting will be held on February 21-22, 1991, at the Hyatt Regency Hotel in Atlanta, Georgia, located at 265 Peachtree Street, NE. This meeting is sponsored by the Centers for Disease Control, and is scheduled to begin at 8:30 a.m. in the Regency Ballroom of the Hyatt Regency Hotel. Registration will begin at 7:30 a.m. on February 21, 1991.

Please keep the following information in mind when planning for your trip to Atlanta.

Air Travel

For those of you who need to make travel arrangements, Fantasy Tours and Travel, our travel agent, will be happy to assist you with your airline reservations. You may contact them at 1-800-876-8687 no later than 10 working days prior to the scheduled meeting date to make your travel arrangements.

Hotel Reservations

The Hyatt Regency is booked during this period, therefore, a partial listing of hotels in Atlanta is enclosed to assist you in making your hotel reservations.

Ground Transportation

The Hyatt is located adjacent to the Peachtree Center station of the MARTA rapid transit system.

The February temperature in Atlanta averages 45 degrees, so you will want to bring warm clothing.

Should you have questions or concerns regarding travel or accommodations, please contact either Ms. Kathy Lane or Mr. Ron Verplaetse at (404) 633-8610.

WE LOOK FORWARD TO SEEING YOU IN ATLANTA!

PACE ENTERPRISES, INC.
CONFERENCE COORDINATORS

"Setting the PACE with leading edge technology"

ATLANTA'S TOP 25 HOTELS

(ranked by number of rooms)

Rank	Hotel	Number of Rooms/Suites	Current Rates Single/Double	Handicapped Facilities	Miles to Airport/Airport Limo Service	Public Trans- portation within Two Blocks
1	Atlanta Marriott Marquis 265 Peachtree Center Ave. Atlanta, GA 30303 (404) 521-0000	1,674 82	\$150.00	yes	10 yes	yes
2	Hyatt Regency Atlanta 265 Peachtree St. Atlanta, GA 30303 (404) 577-1234	1,279 59	\$140.00 \$160.00	yes	9 yes	yes
3	Atlanta Hilton and Towers 255 Courtland St. N.E. Atlanta, GA 30303 (404) 659-2000	1,224 60	\$155.00 \$180.00	yes	12 yes	yes
4	The Westin Peachtree Plaza 210 Peachtree St. Atlanta, GA 30343 (404) 659-1400	1,074 50	\$140.00 \$205.00	yes	10 no	yes
5	Radisson Hotel Atlanta Courtland Street and International Boulevard Atlanta, GA 30343 (404) 659-6500	754 150	\$89.00 \$145.00	no	10 no	yes
6	Atlanta Airport Marriott 4711 Best Road College Park, GA 30337 (404) 766-7900	642 21	\$98.00 \$118.00	yes	1.5 no	no
7	The Ritz-Carlton, Buckhead 3434 Peachtree Road N.E. Atlanta, GA 30326 (404) 237-2700	521 29	\$135.00 \$160.00	yes	15 yes	yes
(tie)	Stouffer Waverly Hotel 2450 Galleria Parkway Atlanta, GA 30339 (404) 953-4500	521 29	\$140.00 \$200.00	yes	21 yes	yes
9	Atlanta Airport Hilton 1031 Virginia Ave. Hapeville, GA 30354 (404) 767-9000	501 4	\$115.00 \$150.00	yes	1 no	no
10	Ramada Renaissance Hotel 4736 Best Road College Park, GA 30337 (404) 762-7676	500 57	\$110.00 \$125.00	yes	1 yes	yes
11	Hyatt Regency Ravinia 4355 Ashford-Dunwoody Road Atlanta, GA 30346 (404) 395-1234	492 41	\$115.00 \$165.00	yes	20 yes	yes
12	Pierremont Plaza Hotel & Conference Center 590 West Peachtree St. N.W. Atlanta, GA 30308 (404) 881-6000	481 24	\$89.00 \$104.00	no	17 no	yes
13	Omni Hotel at CNN Center 100 CNN Center Atlanta, GA 30335 (404) 659-0000	469 30	\$145.00 \$165.00	yes	8 yes	yes
14	Colony Square Hotel 1175 Peachtree St. Atlanta, GA 30361 (404) 892-6000	466 34	\$92.00 \$102.00	yes	23 yes	yes
(tie)	Holiday Inn Downtown Atlanta 175 Piedmont Ave. Atlanta, GA 30303 (404) 659-2727	466 7	\$79.00 \$98.00	yes	10 yes	yes

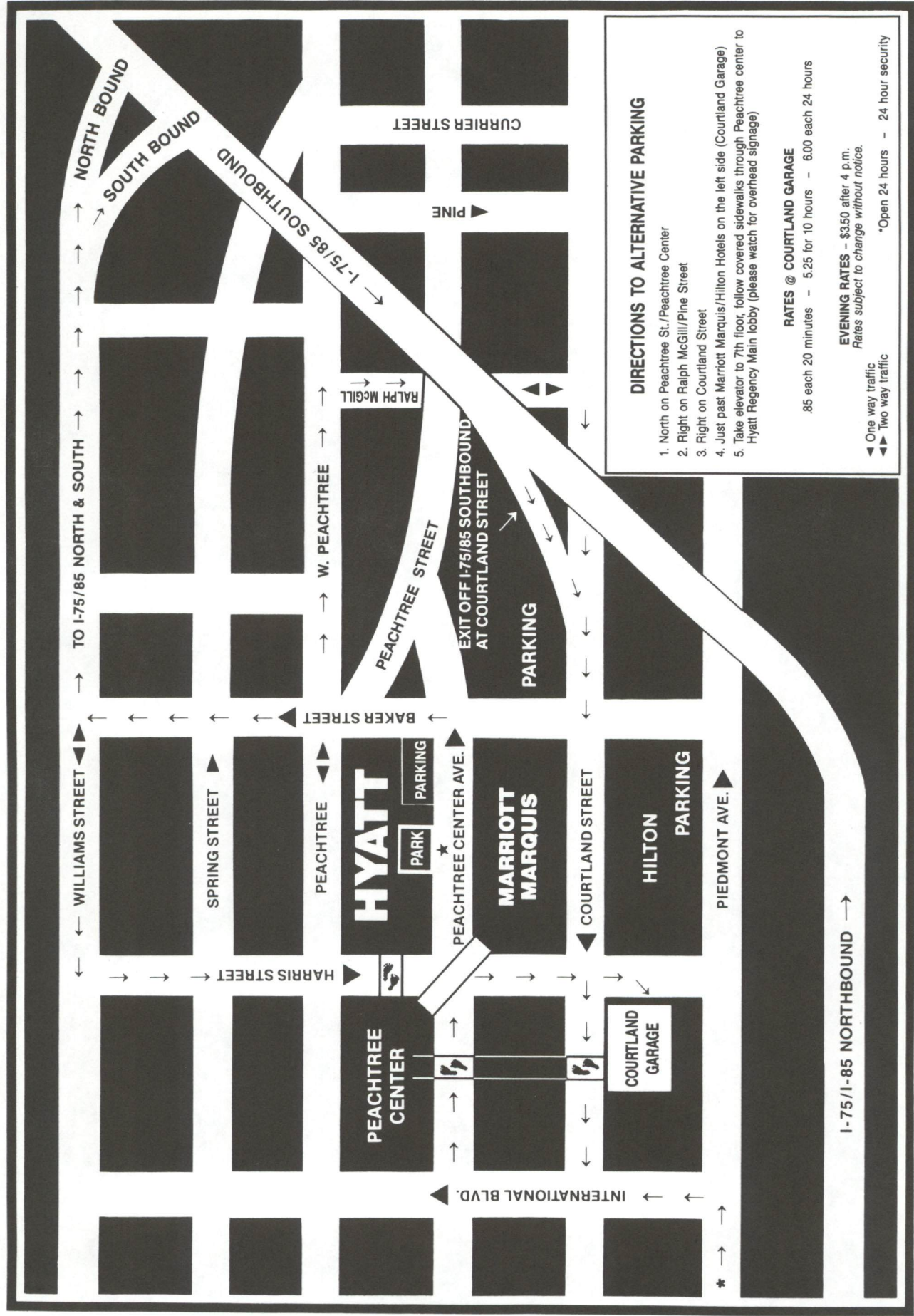
ATLANTA'S TOP 25 HOTELS

(ranked by number of rooms)

Rank	Hotel	Number of Rooms/Suites	Current Rates Single/Double	Handicapped Facilities	Miles to Airport/Airport Limo Service	Public Trans- portation within Two Blocks
16	The Ritz-Carlton, Atlanta 181 Peachtree St. NE Atlanta, GA 30303 (404) 659-0400	454 22	\$135.00 \$199.00	yes	8 yes	yes
17	Atlanta Marriott Northwest 200 Interstate North Parkway Atlanta, GA 30339 (404) 952-7900	403 2	\$98.00 \$110.00	yes	20 yes	no
18	Atlanta Marriott Perimeter Center 246 Perimeter Center Parkway Atlanta, GA 30346 (404) 394-6500	402 4	\$42.00 \$112.00	yes	20 no	yes
19	Ramada Hotel Capitol Plaza 450 Capitol Ave. Atlanta, GA 30312 (404) 688-1900	400 14	\$62.00 \$77.00	yes	7 yes	yes
20	Hyatt Atlanta Airport 1900 Sullivan Road College Park, GA 30337 (404) 991-1234	399 8	\$105.00 \$120.00	yes	1 no	yes
21	Radisson Inn Dunwoody Interstate 285 at Chamblee-Dunwoody Rd. Atlanta, GA 30341 (404) 394-5000	391 19	\$49.00 \$59.00	yes	38 yes	yes
22	Doubletree Hotel At Concourse Seven Concourse Parkway Atlanta, GA 30328 (404) 395-3900	371 19	\$105.00 \$140.00	yes	25 yes	yes
(tie)	J.W. Marriott Atlanta Lenox Hotel 3300 Lenox Road Atlanta, GA 30326 (404) 262-3344	371 45	\$155.00 \$179.00	yes	20 no	yes
(tie)	Terrace Garden Inn 3405 Lenox Road Atlanta, GA 30326 (404) 261-9250	371 10	\$75.00 \$132.00	yes	21 yes	yes
25	Radisson Inn & Conference Center Interstate 75 at Howell Mill Road Atlanta, GA 30318 (404) 351-6100	365 22	\$55.00 \$65.00	yes	13 yes	yes
(tie)	Sheraton Atlanta Airport Hotel 1325 Virginia Ave. Atlanta, GA 30344 (404) 768-6660	365 12	\$64.00 \$94.00	no	1 yes	no

SOURCE: 1990-1991 Convention Planner, Atlanta Convention and Visitors Bureau.

LOCAL PARKING AND INTERSTATE ACCESS MAP



★ DIRECTIONS TO INTERSTATE 75/85: TURN LEFT OUT OF THE MOTOR LOBBY ONTO PEACHTREE CENTER AVENUE. TAKE THE FIRST LEFT ONTO BAKER STREET. AT THE THIRD TRAFFIC LIGHT, TURN RIGHT ONTO WILLIAMS STREET. THIS WILL LEAD TO THE 75/85 ACCESS IN THREE BLOCKS. BEAR LEFT FOR 75/85 NORTHBOUND OR RIGHT FOR 75/85 SOUTHBOUND.

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"CORRESPONDENCE TRACKING"

TYPE: ACTION

DOCUMENT NUMBER: 9120200

FROM: BIXBY, MARY ANN

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 01/31/91

SUBJECT: REQUESTS A GREETING OF CONGRATULATIONS TO DR. BING
FOR A BENEFIT IN HIS HONOR.

ASSIGNED TO: Rachel Levinson

ACTION REQUIRED: REVIEW/COMMENT DAB

SENDER'S DUE DATE: OSTP DUE DATE: 02/08/91

DATE COMPLETED: -----

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 01/31/91

FILE: *p* LIFE SCIENCES

THE WHITE HOUSE

WASHINGTON

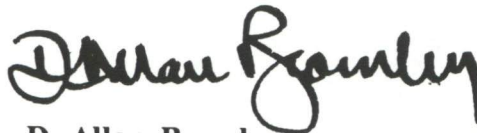
February 7, 1991

Dear Dr. Bing:

It is a pleasure to me to extend to you my personal greetings and congratulations on the occasion of this special celebration.

There are few, indeed, who achieve national, let alone international distinction in two quite different disciplines. You have earned and deserve the heartfelt thanks of us all for your magnificent contributions to science and to the humanities.

Sincerely yours,

A handwritten signature in dark ink, appearing to read "D. Allan Bromley". The signature is fluid and cursive, with the first name "D. Allan" and the last name "Bromley" clearly distinguishable.

D. Allan Bromley
Assistant to the President
for
Science and Technology

Dr. Richard Bing
Huntington Medical Research Institutes
734 Fairmount Avenue
Pasadena, California 91105

"CORRESPONDENCE TRACKING"

TYPE: Action Item

DOCUMENT NUMBER: 9120200

FROM: BIXBY, Mary Ann; Huntinton Medical Res. Inst, Pasadena, CA

TO: DAB

DATE OF
CORRESPONDENCE: 01/31/91

SUBJECT: Requests a Greeting of Congratulations to Dr. Bing
for a Benefit in his Honor.

ASSIGNED TO: D.A. Henderson

ACTION REQUIRED: Comments to DAB

SENDER'S DUE DATE: OSTP DUE DATE: 02/08/91

DATE COMPLETED: 02/07/91

COPIES TO:

WHITE HOUSE TRACKING #: CONTACT PERSON:

REMARKS:

DATE RECEIVED: 01/31/91
DATE RECEIVED DLS: 02/04/91

FILE: DLS

9120200

HMRI

HUNTINGTON MEDICAL RESEARCH INSTITUTES

January 31, 1991

Hon. D. Allan Bromley
Assistant to the President
for Science and Technology
17th Street and Pennsylvania Ave. N.W.
Washington, D.C. 20506

Dear Dr. Bromley,

This is to request your consideration of sending a greeting of congratulations to Dr. Richard Bing of the Huntington Medical Research Institutes on the occasion of a benefit evening to celebrate his accomplishments in the fields of medicine and music.

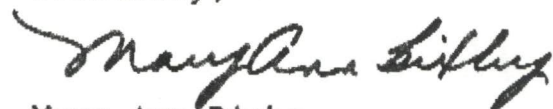
A brief biographical sketch of Dr. Bing accompanies this letter, and I will send additional materials under separate cover, including the feature article which is to appear in the HMRI newsletter February 1.

Presentations to Dr. Bing on the evening of February 16 will include tributes from the German consulate in Los Angeles for his contributions to cardiology in his native Germany, former Secretary of the Air Force Verne Orr who is now serving as chairman of Huntington Memorial Hospital, renowned local music narrator and lecturer Carl Princi who is familiar with Dr. Bing's music, and Dr. Kenneth Shine who is Dean of the School of Medicine at UCLA and himself a cardiologist.

Your greeting would be read during the program for the evening, which is a black tie event at a prestigious Pasadena private social club.

Please call my office with any questions, or if there is more information needed.

Sincerely,



Mary Ann Bixby
Community Relations
Chairman, Benefit Committee

Withdrawal/Redaction Sheet

(George Bush Library)

Document No. and Type	Subject/Title of Document	Date	Restriction	Class.
02. Biography	Biography of Richard John Bing [personal information redacted] (3 pp.)	1/31/91	(b)(6)	

Collection:

Record Group: Bush Presidential Records
Office: Science and Technology Policy, Office of (OSTP)
Series: Bromley, D. Allan, Files
Subseries: General Science Files
WHORM Cat.:
File Location: Life Sciences: General [3 of 4] [1991]

Date Closed:	3/15/2010	OA/ID Number:	62038-003
FOIA/SYS Case #:	2005-0336-F	Appeal Case #:	
Re-review Case #:		Appeal Disposition:	
P-2/P-5 Review Case #:		Disposition Date:	
AR Case #:		MR Case #:	
AR Disposition:		MR Disposition:	
AR Disposition Date:		MR Disposition Date:	

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

Freedom of Information Act - [5 U.S.C. 552(b)]

P-1 National Security Classified Information [(a)(1) of the PRA]
P-2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P-3 Release would violate a Federal statute [(a)(3) of the PRA]
P-4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P-5 Release would disclose confidential advice between the President and his advisors, or between such advisors [(a)(5) of the PRA]
P-6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.

PRM. Removed as a personal record misfile.

(b)(1) National security classified information [(b)(1) of the FOIA]
(b)(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
(b)(3) Release would violate a Federal statute [(b)(3) of the FOIA]
(b)(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
(b)(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
(b)(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
(b)(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
(b)(9) Release would disclose geological or geophysical information

Reservations are limited.
Your reservation includes a tax-deductible donation to
the Huntington Medical Research Institutes of \$100 per person.

Benefit Committee

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Mary Ann Bixby
Judy Bolenbaugh
Ginny Cushman
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Jean Freshwater
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Carolyn Helsper
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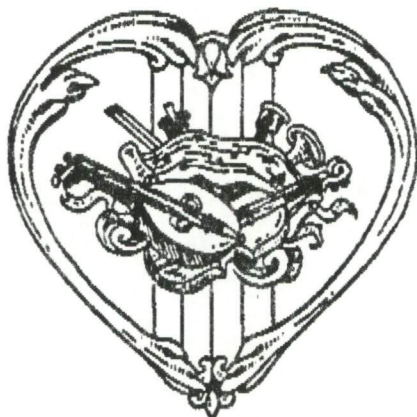
cordially invite you to

Heartstrings

a Dinner-Dance Benefit

to honor

Dr. Richard J. Bing
His Medicine and His Music



Saturday
February 16, 1991
Cocktails 6:30 Dinner 8:00

The Valley Hunt Club
520 S. Orange Grove Boulevard
Pasadena, California

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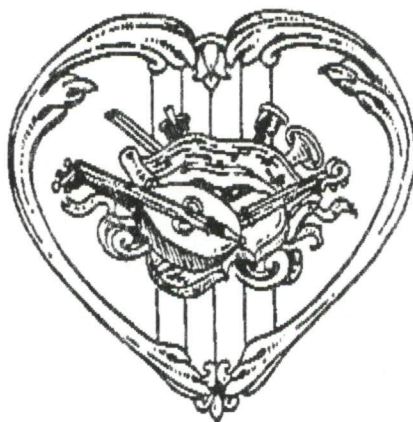
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Richard J. Bing, M.D. Director of Experimental Cardiology Huntington Medical Research Institutes

Heartstrings celebrates the contributions of physician and scientist Dr. Richard Bing to cardiology and to the knowledge of cardiac metabolism which have affected and improved the lives of countless heart patients. His accomplishments as musician and composer are also widely recognized and his music has been played and recorded throughout the world. Dr. Bing joined the staff at Huntington Memorial Hospital and Huntington Medical Research Institutes in 1969. We invite you to participate in our tribute to the illustrious career of this extraordinary man.



\$150 per person

Please reply by
February 7, 1991

Black tie optional

For information:
(818) 397-5447

Heartstrings

STAR-NEWS

PASADENA, CALIFORNIA, TUESDAY, JANUARY 19, 1988

The grace of classical music, paired with the wonder of medicine, keeps doctor...

Inspired by the rhythms of life

BY SELWYN EIBER
Staff Writer

Dr. Richard Bing keeps a photograph of famed aviator Charles Lindbergh and a cassette tape of the orchestral composition "Missa" in his office at Huntington Medical Research Institutes in Pasadena. The 78-year-old director of cardiology and scientific development at HMRI was well acquainted with Lindbergh, and even worked closely with him in the 1930s on a project far apart from airplanes.

He also is quite familiar with "Missa," which means the Mass. He com-

posed it himself in 1979.

"I couldn't make up my mind whether to go into medicine or music," recalled Bing in a recent interview.

But medicine won out, and it was his early interest in tissue culture that brought him in contact with Lindbergh.

The former airmail pilot astounded the world in 1927 when he made the first solo, nonstop transatlantic flight from New York to Paris aboard The Spirit of St. Louis.

But Lindbergh, like Bing, didn't stick to one field.

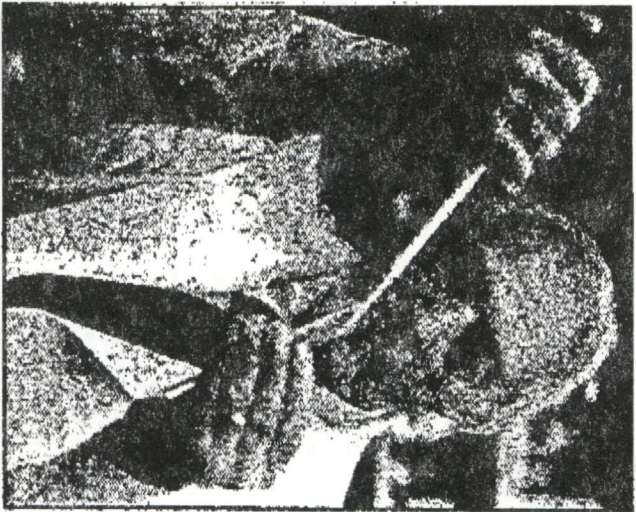
Lindbergh wanted to create an artificial heart that could circulate blood

through a body while surgeons worked repair the real heart. His sister-in-law had died because no such bypass put system had been invented yet (and won not be until 1953).

Bing, along with experimental surgeon Dr. Alexis Carrel, was asked to work the project, which resulted in a put that proved useful for researchers who wanted to study organs for days and even weeks at a time.

Bing said Lindbergh was a visionary with his artificial heart concept.

Please see BIN
Page A



Raleigh Souther / Star-News
Heart specialist Dr. Richard Bing

Bing: Diverse interests complete the me

Continued from Page A-1

"He had a very direct, almost naive mind," Bing said.

Bing remembers that when they first met, Lindbergh was very shy, but nevertheless had a great sense of humor. "He was never, never, never a stuffed shirt."

Bing also was not shocked or put off by a pilot dabbling in medical research.

"I always thought each individual should be judged by what they're doing and not their training."

When Lindbergh visited Bing and his family many years later, the flier had become much more personable.

"My daughter adored him. She was a teenager. I said 'Go out and see him.' She was absolutely enthralled."

Aside from medical pursuits, which have won him numerous awards, Bing has done much more than occasionally dabble in music.

At the age of 11, he was already playing one of Schubert's sonatas in the renowned St. Catherine's Church, which was then called the Meistersinger Church in Nuremberg, West Germany.

At 14, he began writing orchestral compositions while studying at the Hochschule Conservatory of Music in Frankfurt, West Germany, and he has continued to study and write music over the years.

While music and medicine may seem to be worlds apart, Bing sees many similarities.

"What always should shine through in every piece of music is your soul. Well, I'm a cardiologist, so I'll say your heart."

The heart, Bing believes, also should play

a role in medicine.

"In medicine, you should have an emotional involvement with the patient," he said, denouncing physicians who prefer a detached style. "You should have full empathy."

"When the work is not very good, or I feel that research doesn't quite fulfill me, then I turn to music. It's a different side of the crystal." In both medicine and music, "we search for some of the secrets of nature."

Even though Bing is fast approaching 80, he has no intention of retiring or slowing down.

"I do think I work just as hard now as I ever did," he said.

Later this month, a London journal called *The Bioscience Reports* will publish his latest article, which describes how cells can be made to produce substances that dilate blood vessels to improve blood flow through the heart.

And in April, he will receive an honorary degree from the University of Bologna in Italy, primarily for his pioneering work in cardiac metabolism. He was the prime founder and first president of the International Society of Heart Research.

Meanwhile, Bing is writing a symphony that focuses on two opposite and powerful emotions.

One part of the work is inspired by deeply introspective poems sent to him by a nun, who is the daughter of one of his patients. The second part is based on the bawdy play "Lysistrata," by the ancient Greek playwright Aristophanes.

Yet again, Bing is combining different sides of the same crystal.



Richard Schickel

"When the work is not very good, or I feel that research does quite fulfill me, then I turn to music. It's a different side of crystal."

— Dr. Rich



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HMRI

HUNTINGTON MEDICAL RESEARCH INSTITUTES

FACSIMILE TRANSMITTAL

Date 1/31/91
Attention Hon. D. Allan Bromley
Department Asst. to President
Sci. & Technology
Company _____
To FAX # 202-395-3261
From Mary Ann Bixby

Description of Material or Comments:

Greeting request

Pages (including this cover sheet): 2

IF TRANSMITTAL IS NOT CLEAR OR IF PAGES ARE MISSING, PLEASE CALL (818) 397-5436

Our FAX Number: (818) 397-3330

"CORRESPONDENCE TRACKING"

TYPE: ACTION

DOCUMENT NUMBER: 9120346

FROM: FLANNAK, FRED AND JEANNE

TO: DR. BROMLEY

DATE OF
CORRESPONDENCE: 01/29/91

SUBJECT: SCOLIOSIS RESEARCH

ASSIGNED TO: Life Sciences

ACTION REQUIRED: DIRECT REPLY

SENDER'S DUE DATE:

OSTP DUE DATE:

02/28/91

DATE COMPLETED:

COPIES TO:

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 02/08/91

FILE: 8- LIFE SCIENCES SCOLIOSIS

18011003

"CORRESPONDENCE TRACKING"

TYPE: Action Item

DOCUMENT NUMBER: 9120346

FROM: FLANNAK, Fred and Jeanne; Newark, DE

TO: DAB

DATE OF
CORRESPONDENCE: 01/29/91

SUBJECT: Trying for 12 years to get research support from NIH
for their scoliosis research.

ASSIGNED TO: Rachel Levinson

ACTION REQUIRED: Direct Reply

SENDER'S DUE DATE: OSTP DUE DATE: 02/28/91

DATE COMPLETED: 02/13/91

COPIES TO:

WHITE HOUSE TRACKING #:

CONTACT PERSON:

REMARKS:

DATE RECEIVED: 02/08/91
DATE RECEIVED DLS: 02/12/91

FILE: DLS

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

February 13, 1991

Dear Drs. Lannak:

As the Assistant Director for Life Sciences, Dr. Bromley has asked me to respond to your January 29 letter regarding the difficulties you have encountered with the research grant application process at the National Institutes of Health. The Office of Science and Technology Policy (OSTP) does not conduct or support research. It is the mission of the Office of Science and Technology Policy is to provide the President and the White House with the best scientifically-based advice on policy decisions.

As the attachment to your letter shows, the National Institutes of Health is part of the Public Health Service (PHS) in the Department of Health and Human Services. The head of PHS is Dr. James O. Mason, and I suggest that you contact him directly. His mailing address is Dr. James O. Mason, Assistant Secretary for Health, Department of Health and Human Services, Room 716G, Hubert Humphrey Building, 200 Independence Avenue, S.W., Washington, D.C. 20201.

Sincerely yours,



Rachel E. Levinson
Assistant Director
for
Life Sciences

Dr. Fred Lannak
Dr. Jeanne Lannak
206 Mederia Circle
Newark, Delaware 19702

346

January 29, 1991

RECEIVED

D. Allan Bromley
Assistant to the President
1600 Pennsylvania Avenue, N.W.
Washington, D.C. 20500

91 FEB 8 P4:37

OFFICE OF THE
DIRECTOR

Dear D. Allan Bromley:

We are asking you to help us because the National Institutes of Health (NIH) is part of the Executive Branch of the U.S. Government.

Please send us the name of a person at the NIH who will help us with our Scoliosis Research (Curved Spinal Column Research). We are looking for a person at the NIH who can direct us to other people at the NIH who will help us with our Scoliosis Research.

President Bush got upset and declared war on Iraq on January 15, 1991 because their President Saddam Hussein would not comply with President Bush's wishes concerning a short period of time, five months between August 7, 1990 and January 15, 1991.

We took our Scoliosis Research to the NIH in Bethesda, Maryland in 1979 for the first time. It is now twelve years later and we are still looking for the right department to communicate with about our Scoliosis Research, at the NIH.

We have received numerous replies from many important people at the NIH over the last twelve years about our Scoliosis Research. The problem is, every time that we call the NIH back about a reply that they send us concerning our Scoliosis Research, it always turns into nothing more than a dead end street. No one at the NIH ever knows what to do with our Scoliosis Research information.

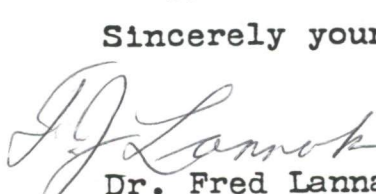
The NIH sent us at least a dozen of their Research Applications during the last twelve years. The NIH Research Applications are very difficult for two people like us to understand. We wrote the NIH many letters and called them numerous times to ask them questions about the Research Applications. The answers that we received from our letters and telephone calls to the NIH about the Research Applications added up to zero. No one at the NIH ever answered any of our questions.

Every person that we talk or write to at the NIH either does not have the authority to deal with our Scoliosis Research or refers us to someone else who does not have the authority to deal with our Scoliosis Research.

Please help us find a Scoliosis Research information center at the NIH. We need to find a department at NIH that is able to direct us to people that can help us with our Scoliosis Research.

Your concern in this matter is appreciated.

Sincerely yours.


Dr. Fred Lannak & Dr. Jeanne Lannak
206 Mederia Circle
Newark, DE 19702

U.S. GOVERNMENT MANUAL
EXECUTIVE OFFICE OF THE PRESIDENT
THE PRESIDENT OF THE UNITED STATES GEORGE BUSH

"The President is the administrative head of the executive branch of the Government, which includes numerous agencies, both temporary and permanent, as well as the 14 executive departments."

"The Cabinet is composed of the heads of the 14 executive departments—the Secretaries of Agriculture, Commerce, Defense, Education, Energy, Health and Human Services, Housing and Urban Development, Interior, Labor, State, Transportation, Treasury, and Veterans Affairs, and the Attorney General—and certain other executive branch officials to whom the President accords Cabinet rank."

"The Secretary of Health and Human Services... directs Department staff in carrying out the approved programs and activities of the Department and promotes general public understanding of the Department's goals, programs, and objectives. The Secretary administers these functions through the Office of the Secretary and the five Operating Divisions, which include: the Social Security Administration, the Health Care Financing Administration, the Office of Human Development Services, the Public Health Service, and the Family Support Administration."

The National Institutes of Health (NIH) is a subdivision of the Public Health Service. The enclosed copies from the U.S. GOVERNMENT MANUAL indicates that a large number of the Public Health Service subdivisions place a strong emphasis on research.

Why are we having such a difficult time finding someone at the NIH who will assist us with our Scoliosis Research? What have we been doing wrong for the past twelve years that is preventing the NIH from helping us with our Scoliosis Research? Is there an unwritten law at the NIH that excludes us because we have chiropractic degrees?

The Public Health Service subdivisions on the enclosed pages uses the word research at least 106 times. The NIH may be confused when we speak to them about our Scoliosis Research because they hear the word research dozens of times every day in a large variety of ways.

On January 15, 1991 President Bush gave President Saddam Hussein a reason why America was going to attack Iraq. Why won't the NIH give us a reason for not helping us with our Scoliosis Research for the last twelve years?

FAMILY SUPPORT ADMINISTRATION

370 L'Enfant Promenade, SW., Washington, DC 20447
phone, 202-252-4500

Assistant Secretary

Deputy Assistant Secretary

Director, Office of Family Assistance

Director, Office of Child Support Enforcement

Director, Office of Community Services

Director, Office of Refugee Resettlement

Associate Administrator, Office of Financial

Associate Management

Associate Administrator, Office of Program Management

Evaluation

Associate Administrator, Office of Management Evaluation

Associate Administrator, Sales and Information Systems

Associate Administrator, Office of
and Information Systems

Associate Administrator Communications

JO ANNE B. BARNHART

LAURENCE LOVE, Acting

JASON TURNER

JO ANNE B. BARNHART

EUNICE THOMAS

CHRISTOPHER GERSTON

MICHAEL STURMAN

HOWARD ROLSTON

NAOMI B. MARR

BARBARA CEBU HAR

The Department of Health and Human Services is the Cabinet-level department of the Federal executive branch most concerned with people and most involved with the Nation's human concerns. In one way or another—whether it is mailing out social security checks or making health services more widely available—HHS touches the lives of more Americans than any other Federal agency. It is literally a department of people serving people, from newborn infants to our most elderly citizens.

The Department of Health, Education, and Welfare was created on April 11, 1953. The Department was redesignated as the Department of Health and Human Services (HHS), effective May 4, 1980, by the Department of Education Organization Act (20 U.S.C. 3508).

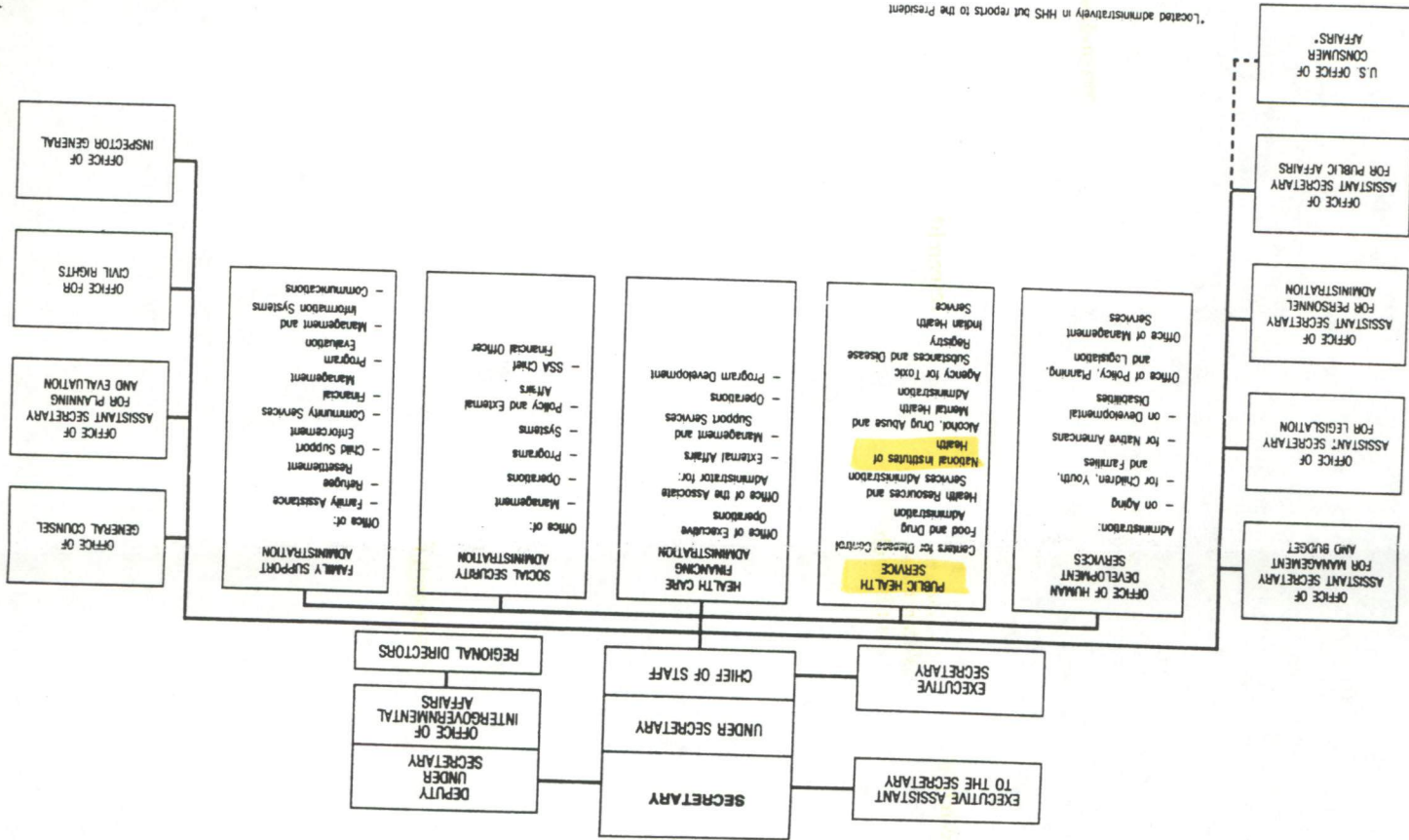
Public Health Service, and the Family Support Administration.

The Under Secretary, the Assistant Secretaries, the General Counsel, the Inspector General, and other senior officials aid the Secretary with the overall management responsibilities of the Department.

Since the Secretary is accountable to the Congress and the public for the way the Department spends taxpayers' money, the Secretary and top staff spend a considerable amount of time testifying before committees of the Congress, making speeches before national organizations, and meeting with the press and the public to explain HHS actions.

Office of the Secretary

The Secretary of Health and Human Services advises the President on health, welfare, and income security plans, policies, and programs of the Federal Government. The Secretary directs Department staff in carrying out the approved programs and activities of the Department and promotes general public understanding of the Department's goals, programs, and objectives. The Secretary administers these functions through the Office of the Secretary and the five Operating Divisions, which include: the Social Security Administration, the Health Care Financing Administration, the Office of Human Development Services, the



formulation, development, implementation, and review of legislation and policies affecting persons with developmental disabilities;

- serves as the primary agency within the Office of Human Development Services on all issues concerning people with developmental disabilities.

- advocates for the needs of people with disabilities in Office program planning and policy development; and
- develops standards, provides technical assistance, issues best practices guidelines, and initiates policy relative to Office programs for persons with developmental disabilities.

For further information, contact the Commissioner, Administration on Developmental Disabilities. Phone, 202-245-2890.

Public Health Service

[For the Public Health Service statement of organization, see the *Federal Register* of Dec. 2, 1977, 42 FR 61317]

The Public Health Service has its origin in an act of July 16, 1798 (ch. 77, 1 Stat. 605), authorizing marine hospitals for the care of American merchant seamen.

Subsequent legislation has vastly broadened the scope of its activities.

The Public Health Service Act of July 1, 1944 (42 U.S.C. 201), consolidated and revised substantially all existing legislation relating to the Public Health Service. The basic Public Health Service legal responsibilities have been

broadened and expanded many times since 1944. Major organizational changes have occurred within the Public Health Service to support its mission to promote the protection and advancement of the Nation's physical and mental health. This is accomplished by:

- coordinating with the States to set and implement national health policy and pursue effective intergovernmental relations;

- generating and upholding cooperative international health-related agreements, policies, and programs;

- conducting medical and biomedical

the quality of patient care services, the Agency promotes improvements in clinical practice and patient outcomes through more appropriate and effective health care services; improvements in the financing, organization, and delivery of health care services; and increased access to quality health care.

The Agency acquires, develops, and transfers new knowledge through a coordinated program of research, demonstrations, evaluations, and information dissemination activities. Generally, the Agency's primary functions are:

- developing a broad base of scientific research, methods, and databases through extramural research grants and contracts and intramural research activities;

- demonstrating and evaluating new ways to organize, finance, and direct health care services to improve the delivery, access to, and outcomes of such services;

- assessing technologies being considered for reimbursement by federally funded programs;

- facilitating the development of practice guidelines and standardized measures of quality care for use by physicians and other health care practitioners; and

- promoting the use of health services research findings through systematic, broad-based information dissemination.

The Agency supports research in medical treatment effectiveness and patient outcomes; assessment of health care technologies; medical malpractice and liability; delivery of health services in rural areas; availability, accessibility, and quality care for underserved populations; alternative delivery systems, providers, and practice patterns in primary care; and resource use, cost of care, and delivery of services to persons with human immunodeficiency virus-related (HIV) illnesses.

For further information, call 301-443-4100.

Alcohol, Drug Abuse, and Mental Health Administration

The mission of the Alcohol, Drug Abuse, and Mental Health Administration is to

provide a national focus for the Federal effort to increase knowledge and to promote effective strategies in handling health problems and issues associated with the use and abuse of alcohol and drugs, and with mental illness and mental health.

In carrying out these responsibilities, the Administration:

- conducts and supports research on the biological, psychological, behavioral, and epidemiological aspects of alcoholism, drug abuse, and mental health and illness;

- supports the training of scientists to conduct research in alcoholism, drug abuse, and mental health treatment and prevention services;

- gathers and analyzes data about the extent of alcohol, drug abuse, and mental health problems and the national response to these needs in terms of planning, establishing, and evaluating alcoholism, drug abuse, and mental health programs;

- administers the alcohol, drug abuse, and mental health services block grant program and collaborates with, provides assistance to, and encourages other Federal agencies and national, foreign, State, and local organizations, as well as hospitals and voluntary groups to facilitate and expand programs for the prevention and treatment of alcohol, drug abuse, and mental health problems; and

- provides information on alcoholism, drug abuse, and mental health to the public and to the scientific community.

For further information, call 301-443-3875.

Major Components

National Institute on Alcohol Abuse and Alcoholism

The Institute provides a national focus for the Federal effort to increase knowledge and promote effective strategies to deal with health problems and issues associated with alcohol abuse and alcoholism. In carrying out these responsibilities, the Institute:

- conducts and supports research on alcohol-related disorders in its own laboratories and through extramural

—conducts epidemiological studies and national and community surveys to assess the risks for alcohol abuse among various population groups;

—plans, directs, supports, and evaluates research to identify new and improved alcoholism prevention, intervention, and treatment methods and techniques for application in the Nation's health care system;

—supports training and development of scientists for participation in alcohol research programs and activities;

—collaborates with other research institutes and Federal programs relevant to alcohol abuse and alcoholism and provides coordination of Federal alcohol abuse and alcoholism research activities; —serves as a national resource for the collection, analysis, and dissemination of scientific findings and improved methods of alcoholism prevention and treatment services;

—maintains continuing relationships with institutions and professional associations and with international, national, State, and local officials and voluntary agencies and organizations engaged in alcohol related work;

—conducts policy studies and activities that have broad implications for alcoholism treatment, prevention, and rehabilitation activities;

—performs data collections and analysis and provides both technical assistance and technology transfer to State and local governments and community and voluntary organizations in the areas of policy development, program assessment, establishment of treatment standards, accreditation, and resource utilization; and

—supports public education activities to inform the public of the risks and consequences associated with alcohol abuse and alcoholism.

For further information, call 301-443-4373.

National Institute on Drug Abuse The Institute provides a national focus for the Federal effort to increase knowledge and promote effective strategies in dealing with health problems and issues associated with drug abuse. In carrying

—conducts and supports research on the biological, psychological, and psychosocial aspects of the condition, epidemiology, treatment, and prevention of drug abuse and addiction;

—supports research training and career development of individuals and institutions that are training individuals for participation in drug abuse research programs and activities;

—works with States to provide technical assistance and national leadership in the areas of data collection, treatment outcome and effectiveness, and health services research;

—collaborates with the Office for Substance Abuse Prevention and the Office for Treatment Improvement to encourage Federal agencies, national, foreign, State, and local organizations, as well as hospitals and volunteer groups to facilitate and extend programs for the prevention of drug abuse and addiction, and the care, treatment, and rehabilitation of drug abusers; and —carries out administrative and financial management, policy and program development, planning and evaluation, and public information functions that are required to implement such programs.

For further information, call 301-443-6487.

National Institute of Mental Health

The Institute provides a national focus for the Federal effort to increase knowledge and advance effective strategies to deal with health problems and issues in the promotion of mental health and the prevention and treatment of mental illness.

In carrying out these responsibilities, the Institute:

—conducts and supports research and research training on the biological, psychological, behavioral, and epidemiological aspects of mental health and illness;

—conducts and supports research on the development and improvement of mental health services and prevention programs and on their administration and financing;

—collaborates with and provides technical assistance and data to State and

sub-State authorities to assist them in planning, establishing, maintaining, coordinating, and evaluating more effective mental health programs;

—collaborates with, provides assistance to, and encourages other Federal agencies, national, foreign, State, and local organizations, as well as hospitals, professional associations, and volunteer groups to facilitate and extend programs to promote mental health and prevent mental illness and to provide for the care, treatment, and rehabilitation of mentally ill persons;

—collects, analyzes, and disseminates scientific findings and data on the incidence, prevalence, and resources for the treatment of mental illness; and

—carries out administrative and financial management, policy development, planning and evaluation, and public information functions that are required to implement such programs.

For further information, call 301-443-3877.

Office for Substance Abuse Prevention

The Office provides a national focus for the Federal effort to prevent alcohol abuse and other drug problems. In carrying out this responsibility, the Office:

—develops, implements, and reviews prevention and health promotion policy related to alcohol and drug abuse, analyzing the impact of Federal activities on State and local governments and private program activities;

—supports comprehensive, collaborative, community-based innovative prevention demonstration programs;

—operates a grant program for projects to demonstrate effective models for the prevention, early intervention, and treatment of drug and alcohol abuse among high-risk youth and other target populations;

—sponsors regional and national workshops and conferences on the prevention of drug and alcohol abuse; —supports the training for substance abuse counselors and other health professionals involved in drug and alcohol abuse education, prevention, and intervention;

—provides technical assistance to States and local authorities and other national organizations and groups in planning, establishing, and maintaining substance abuse prevention efforts;

—collects and compiles drug and alcohol abuse prevention literature and other materials and supports a clearinghouse to disseminate such materials among States, political subdivisions, educational agencies and institutions, health and drug treatment networks, and the general public;

—serves as a national authority and resource for developing and analyzing information and findings relating to the prevention alcohol and drug abuse;

—participates in the dissemination and implementation of research findings by PHS agencies and other research institutes on the prevention of alcohol and drug abuse;

—collaborates with and encourages other Federal agencies, national, foreign, State, and local organizations to promote substance abuse prevention activities;

—provides and promotes the evaluation of projects; and

—carries out administrative and financial management, policy and program development, planning and evaluation, and public information functions which are required to implement such programs.

For further information, call 301-443-5266.

Office for Treatment Improvement

The principal function of the Office is to provide national leadership for the Federal effort to enhance approaches and programs focusing on the treatment of drug abusers as well as associated problems of alcoholism and mental illness among this population. In carrying out this responsibility, the Office:

—collaborates with States, communities, health care providers, and national organizations to upgrade the quality of drug treatment, to improve the effectiveness of drug treatment programs, and to expand drug treatment capacity; provides financial assistance to targeted geographic areas to strengthen treatment programs for drug abuse and other related disorders (with emphasis on

assistance for pregnant and postpartum women and their infants, minorities, adolescents, and residents of public housing projects), and to strengthen the collaboration among the members of the drug treatment community;

- provides a focus for addressing the treatment needs of individuals with multiple drug, alcohol, and mental problems;

- collaborates with the National Institute on Drug Abuse and the States to promote development of treatment outcome standards;

- collaborates with the Institutes and the Office for Substance Abuse Prevention in treatment data collection and training of health care providers;

- promotes mainstreaming of alcohol, drug abuse, and mental health treatment into the health care system; and

- administers the alcohol, drug abuse, and mental health services block grant program and the homeless block grant program, including compliance reviews, technical assistance to States, territories, and Indian tribes, and application and reporting requirements related to the block grant programs.

For further information, call 301-443-6501.

Centers for Disease Control

The Centers for Disease Control, established as an operating health agency within the Public Health Service by the Secretary of Health, Education, and Welfare on July 1, 1973, is the Federal agency charged with protecting the public health of the Nation by providing leadership and direction in the prevention and control of diseases and other preventable conditions and responding to public health emergencies. It is composed of nine major operating components: Epidemiology Program Office, International Health Program Office, Public Health Practice Program Office, Center for Prevention Services, Center for Environmental Health and Injury Control, National Institute for Occupational Safety and Health, Center for Chronic Disease Prevention and Health Promotion, Center for Infectious

Diseases, and the National Center for Health Statistics.

The agency administers national programs for the prevention and control of communicable and vector-borne diseases and other preventable conditions. It develops and implements programs in chronic disease prevention and control, including consultation with State and local health departments. It develops and implements programs to deal with environmental health problems, including responding to environmental, chemical, and radiation emergencies.

The agency directs and enforces foreign quarantine activities and regulations; provides consultation and assistance in upgrading the performance of public health and clinical laboratories; organizes and implements a National Health Promotion Program, including a nationwide program of research, information, and education in the field of smoking and health. It also collects, maintains, analyzes, and disseminates national data on health status and health services.

To ensure safe and healthful working conditions for all working people, occupational safety and health standards are developed, and research and other activities are carried out, through the National Institute for Occupational Safety and Health.

The agency also provides consultation to other nations in the control of preventable diseases, and participates with national and international agencies in the eradication or control of communicable diseases and other preventable conditions.

For further information, call 404-639-3286.

Agency for Toxic Substances and Disease Registry

The Agency for Toxic Substances and Disease Registry was established as an operating agency within the Public Health Service by the Secretary of Health and Human Services on April 19, 1983. The Agency's mission is to carry out the health-related responsibilities of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980

(42 U.S.C. 9601), as amended by the Superfund Amendments and Reauthorization Act of 1986, the Resource Conservation and Recovery Act (42 U.S.C. 6901), and provisions of the Solid Waste Disposal Act relating to sites and substances found at those sites and other forms of uncontrolled releases of toxic substances into the environment. The Agency provides leadership and direction to programs and activities designed to protect both the public and workers from exposure and/or the adverse health effects of hazardous substances in storage sites or released in fires, explosions, or transportation accidents.

To carry out this mission, the Agency, in cooperation with States and other Federal and local agencies:

- collects, maintains, analyzes, and disseminates information relating to serious diseases, mortality, and human exposure to toxic or hazardous substances;

- establishes appropriate registries necessary for long-term followup or specific scientific studies;

- establishes and maintains a complete listing of areas closed to the public or otherwise restricted in use because of toxic substance contamination;

- assists, consults, and coordinates with private or public health care providers in the provision of medical care and testing of exposed individuals;

- assists the Environmental Protection Agency in identifying hazardous waste substances to be regulated;

- develops scientific and technical procedures for evaluating public health risks from hazardous substance incidents and for developing recommendations to protect public health and worker safety and health in instances of exposure or potential exposure to hazardous substances; and

- arranges for program support to ensure adequate response to public health emergencies.

For further information, call 404-639-0727.

Food and Drug Administration

The name "Food and Drug Administration" was first provided by the

Agriculture Appropriation Act of 1931 (46 Stat. 392), although similar law enforcement functions had been in existence under different organizational titles since January 1, 1907, when the Food and Drug Act of 1906 (21 U.S.C. 1-15) became effective.

The Food and Drug Administration's activities are directed toward protecting the health of the Nation against impure and unsafe foods, drugs and cosmetics, and other potential hazards.

Center for Drug Evaluation and Research

The Center develops Administration policy with regard to the safety, effectiveness, and labeling of all drug products for human use and reviews and evaluates new drug applications and investigational new drug applications. It develops and implements standards for the safety and effectiveness of all over-the-counter drugs and monitors the quality of marketed drug products through product testing, surveillance, and compliance programs.

The Center coordinates with the Center for Biologics Evaluation and Research regarding activities for biological drug products, including research, compliance, and product review and approval, and develops and promulgates guidelines on Current Good Manufacturing Practices for use by the drug industry. It develops and disseminates information and educational material dealing with drug products to the medical community and the public in coordination with the Office of the Commissioner. It conducts research and develops scientific standards on the composition, quality, safety, and effectiveness of human drugs; collects and evaluates information on the effects and use trends of marketed drug products; monitors prescription drug advertising and promotional labeling to assure their accuracy and integrity; and analyzes data on accidental poisonings and disseminates toxicity and treatment information on household products and medicines.

In carrying out these functions, the Center cooperates with other components of the Administration, other

Public Health Service organizations, governmental and international agencies, volunteer health organizations, universities, individual scientists, nongovernmental laboratories, and manufacturers of drug products.

For further information, call 301-443-2894.

Center for Biologics Evaluation and Research

The Center administers regulation of biological products under the biological product control provisions of the Public Health Service Act and applicable provisions of the Federal Food, Drug, and Cosmetic Act. It provides dominant focus in the Administration for coordination of the Acquired Immune Deficiency Syndrome (AIDS) program, works to develop an AIDS vaccine and AIDS diagnostic tests, and conducts other AIDS-related activities. It inspects manufacturers' facilities for compliance with standards, tests products submitted for release, establishes written and physical standards, and approves licensing of manufacturers to produce biological products.

The Center plans and conducts research related to the development, manufacture, testing, and use of both new and old biological products to develop a scientific base for establishing standards designed to ensure the continued safety, purity, potency, and efficacy of biological products and coordinates with the Center for Drug Evaluation and Research regarding activities for biological drug products, including research, compliance, and product review and approval.

The Center plans and conducts research on the preparation, preservation, and safety of blood and blood products, the methods of testing safety, purity, potency, and efficacy of such products for therapeutic use, and the immunological problems concerned with products, testing, and use of diagnostic reagents employed in grouping and typing blood.

In carrying out these functions, the Center cooperates with other components of the Administration, other Public Health Service organizations, governmental and international agencies,

volunteer health organizations, universities, individual scientists, nongovernmental laboratories, and manufacturers of biological products.

For further information, call 301-496-3556.

Center for Food Safety and Applied Nutrition

The Center conducts research and develops standards on the composition, quality, nutrition, and safety of food and food additives, colors, and cosmetics. It conducts research designed to improve the detection, prevention, and control of contamination that may be responsible for illness or injury conveyed by foods, colors, and cosmetics and coordinates and evaluates the Administration's surveillance and compliance programs relating to foods, colors, and cosmetics.

The Center also reviews industry petitions and develops regulations for food standards to permit the safe use of color additives and food additives; collects and interprets data on nutrition, food additives, and environmental factors affecting the total chemical result posed by food additives; and maintains a nutritional data bank.

For further information, call 202-245-8850.

Center for Veterinary Medicine

The Center develops and conducts programs with respect to the safety and efficacy of veterinary preparations and devices; evaluates proposed use of veterinary preparations for animal safety and efficacy; and evaluates the Administration's surveillance and compliance programs relating to veterinary drugs and other veterinary medical matters.

For further information, call 301-443-3450.

Center for Devices and Radiological Health

The Center develops and carries out a national program designed to control unnecessary exposure of humans to, and ensure the safe and efficacious use of, potentially hazardous ionizing and non-ionizing radiation. It develops policy and priorities regarding Administration programs relating to the safety, effectiveness, and labeling of medical devices for human use; conducts an

the jurisdiction of the Food and Drug Administration are carried out by 6 Regional Field Offices located in the cities of the Department's Regional Offices, through 21 District Offices and 135 Resident Inspection Posts located throughout the United States and Puerto Rico.

For further information, call 301-443-1591. For a listing of Consumer Affairs Offices, see page 322.

Health Resources and Services Administration

The Administration has leadership responsibility in the Public Health Service for general health services and resource issues relating to access, equity, quality, and cost of care.

To accomplish this goal, the Administration:

- supports States and communities in their efforts to plan, organize, and deliver health care, especially to underserved area residents, migrant workers, mothers and children, the homeless, and other groups with special needs;

- participates in the Federal campaign against AIDS by funding service demonstration projects in major cities, establishing centers to train health professionals serving AIDS patients, supporting renovation of health facilities for AIDS patients, and awarding pediatric health care grants;

- provides leadership in improving the education, distribution, quality, and use of the health professionals needed to staff the Nation's health care system;

- tracks the supply of and requirements for health professionals and addresses their competence through the development of a health practitioner data bank;

- monitors developments affecting health facilities and ensures that previously aided institutions honor their commitments to provide uncompensated care;

- administers the National Organ Transplant Act by serving as an information resource on donation, procurement, and transplantation and by promoting other activities designed to increase the availability of organs and tissues;

electronic product radiation control program, including the development and administration of performance standards.

The Center plans, conducts, and supports research and testing relating to medical devices and to the health effects of radiation exposure; and reviews and evaluates medical devices premarket approval applications, product development protocols, and exemption requests for investigational devices. It develops, promulgates, and enforces performance standards for appropriate categories of medical devices and Good Manufacturing Practice regulations for manufacturers; provides technical and other nonfinancial assistance to small manufacturers of medical devices.

The Center develops regulations, standards, and criteria and recommends changes in Administration legislative authority necessary to protect the public health; provides scientific and technical support to other components within the Administration and other agencies on matters relating to radiological health and medical devices; and maintains appropriate liaison with other Federal, State, and international agencies, with industry, and with consumer and professional organizations.

For further information, call 301-443-4690 or 301-427-7163.

National Center for Toxicological Research

The Center conducts research programs to study the biological effects of potentially toxic chemical substances found in the environment, emphasizing the determination of the health effects resulting from long-term, low-level exposure to chemical toxicants and the basic biological processes for chemical toxicants in animal organisms; develops improved methodologies and test protocols for evaluating the safety of chemical toxicants and the data that will facilitate the extrapolation of toxicological data from laboratory animals to man; and develops Center programs as a natural resource under the National Toxicology Program.

For further information, call 501-541-4000.

Regional Operations Field operations for the enforcement of the laws under

- provides direct, personal health services for Hansen's disease patients and other designated beneficiaries;
- assists Federal managers to assure that employees and workplace health factors that increase the Government's productivity are raised to the highest practical level;
- monitors rural health issues and helps coordinate government and private efforts on behalf of rural health facilities;
- processes claims submitted under the National Vaccine Injury Compensation Program; and
- strengthens the public health system by working with State and local public health agencies.

For further information, contact the Associate Administrator for Communications. Phone, 301-443-2086.

Major Components

Bureau of Health Care Delivery and Assistance The Bureau serves as a national focus for efforts to ensure the availability and delivery of health care services in health manpower shortage areas, to medically underserved populations, and to special services populations.

To accomplish this goal, the Bureau:

- provides, through project grants to community-based organizations, funds to meet the health needs of populations in medically underserved areas by supporting the development of primary health care delivery capacity;
- provides, through project grants to State, local, voluntary, public, and private entities, funds to help them meet the health needs of special populations such as migrants, Alzheimer's disease patients, the homeless, and victims of black lung disease;

- administers the National Health Service Corps Program, which recruits and places highly trained health care practitioners for health manpower shortage areas and populations;

- administers the National Health Service Corps Scholarship and Loan Repayment Programs, which provide financial assistance to medical, dental, and nursing students or former students in return for service in health manpower shortage areas;

- designates health manpower shortage and medically underserved areas and populations;

- provides leadership and direction for the Bureau of Prisons Medical Program, the National Hansen's Disease Program, and support for Health Unit No. 1 and the CHAMPUS Program;

- provides on a reimbursable basis comprehensive occupational health consultation and assistance to Federal agencies to enhance productivity and limit employment-related liability through the Federal Employee Occupational Health Program;

- administers a comprehensive health program for designated PHS beneficiaries, including active duty members of the Coast Guard, PHS, and the National Oceanic and Atmospheric Administration.

For further information, contact the Director, Office of Management. Phone, 301-443-2330.

Bureau of Health Professions The Bureau provides national leadership in coordinating, evaluating, and supporting the development and utilization of the Nation's health personnel.

To accomplish this goal, the Bureau:

- serves as a focus for health care quality assurance activities, issues related to malpractice, and the operation of the National Practitioner Data Bank, and the Vaccine Injury Compensation Program;
- supports through grants health professions and nurse training institutions, targeting resources to areas of high national priority such as disease prevention, health promotion, bedside nursing, care of the elderly, and HIV/AIDS;

- funds regional centers that provide educational services and multidisciplinary training for health professions faculty and practitioners in geriatric health care;

- supports programs to increase the supply of primary care practitioners and to improve the distribution of health professionals;

- develops, tests, and demonstrates new and improved approaches to the development and utilization of health personnel within various patterns of

health care delivery and financing systems;

- provides leadership for promoting equity in access to health services and health careers for the disadvantaged;

- administers several loan programs supporting students training for careers in the health professions and nursing;

- funds regional centers to train faculty and practicing health professionals in the counseling, diagnosis, and management of HIV/AIDS infected individuals;

- collects and analyzes data and disseminates information on the characteristics and capacities of U.S. health training systems;

- assesses the Nation's health personnel force and forecasts supply and requirements; and

- in coordination with the Office of the Administrator, Health Resources and Services Administration, serves as a focus for technical assistance activities in the international projects relevant to domestic health personnel problems.

For further information, contact the Information Officer. Phone, 301-443-2060.

Bureau of Maternal and Child Health and Resources Development

The Bureau develops, administers, directs, coordinates, monitors, and supports Federal policy and programs pertaining to health care facilities, health care promotion of mothers and children, a national network of activities associated with organ donations, procurements, and transplantation, and activities related to AIDS. This includes financial, capital, organizational, and physical matters.

To accomplish this goal, the Bureau:

- provides national leadership in supporting, identifying, and interpreting national trends and issues of significance relative to the health status of mothers, infants, children, and children with special health care needs, and administers block and discretionary grants, contracts, and funding arrangements designed to address these issues;

- administers grant, loan, loan guarantee, and interest subsidy programs under titles VI and XVI of the Public Health Service Act, as amended, relating

to the construction, modernization, conversion, or closure of health and health care organizations;

- develops long- and short-range program goals and objectives for health facilities, and for specific health promotional, organ transplantation, and AIDS activities;

- promotes reduction of costs associated with facility design, construction, modernization, and replacement, and nonmedical operations such as energy and maintenance;

- develops, conducts, and maintains a program of grants to organ procurement organizations;

- serves as adviser to and coordinates activities with other administration organizational elements, other Federal organizations within and outside the Department, State and local bodies, and professional and scientific organizations;

- develops, promotes, and directs efforts to improve the management, operational effectiveness, and efficiency of health care systems, organizations, and facilities;

- provides technical assistance to organ procurement organizations and health care delivery systems and facilities in a wide variety of specific technical and technological systems;

- administers regional facilities engineering and construction activities performed by Public Health Service Regional Offices; and

- maintains liaison and coordinates with non-Federal public and private entities as necessary for the accomplishment of its missions and objectives.

For further information, contact the Information Officer. Phone, 301-443-3376.

Indian Health Service

The Indian Health Service provides a comprehensive health services delivery system for American Indians and Alaska Natives with opportunity for maximum tribal involvement in developing and managing programs to meet their health needs. The Service's goal is to raise the health level of the Indian and Alaska

Native people to the highest possible level.

To carry out its mission and to attain its goal, the Service:

- assists Indian tribes in developing their health programs through activities including health management training, technical assistance, and human resource development;

- facilitates and assists Indian tribes in coordinating health planning, in obtaining and utilizing health resources available through Federal, State, and local programs, in operating comprehensive health programs, and in health program evaluation;

- provides comprehensive health care services, including hospital and ambulatory medical care, preventive and rehabilitative services, and development of community sanitation facilities; and

- serves as the principal Federal advocate for Indians in the health field to assure comprehensive health services for American Indians and Alaska Natives.

For further information, contact the Information Coordinator. Phone, 301-443-1397.

National Institutes of Health

The mission of the National Institutes of Health is to improve the health of the American people. To carry out this mission, the agency conducts and supports biomedical research into the causes, prevention, and cure of diseases; supports research training and the development of research resources; and makes use of modern methods to communicate biomedical information.

Major Components

National Cancer Institute Research on cancer is a high priority program as a result of the National Cancer Act, which made the conquest of cancer a national goal. The Institute developed a National Cancer Program to expand existing scientific knowledge on cancer cause and prevention as well as on the diagnosis, treatment, and rehabilitation of cancer patients.

Research activities conducted in the Institute's laboratories or supported through grants or contracts include many investigative approaches to cancer,

including chemistry, biochemistry, biology, molecular biology, immunology, radiation physics, experimental chemotherapy, epidemiology, biometry, radiotherapy, and pharmacology. Cancer research facilities are constructed with Institute support, and training is provided under university-based programs. The Institute, through its cancer control element, applies research findings as rapidly as possible in preventing and controlling human cancer.

For further information, call 301-496-5737.

National Heart, Lung, and Blood Institute

The Institute provides leadership for a national program in diseases of the heart, blood vessels, blood, and lungs, and in the use of blood and the management of blood resources.

It conducts studies and research into the clinical use of blood and all aspects of the management of blood resources, and supports training of manpower in fundamental science and clinical disciplines for participation in basic and clinical research programs relating to heart, blood vessel, blood, and lung diseases.

It coordinates with other research institutes and with all Federal agency programs relating to the above diseases, including programs in hypertension, stroke, respiratory distress, and sickle cell anemia.

The Institute plans, conducts, fosters, and supports an integrated and coordinated program of research, investigations, clinical trials and demonstrations relating to the causes, prevention, methods of diagnosis and treatment (including emergency medical treatment) of heart, blood vessel, lung, and blood diseases through research performed in its own laboratories and through contracts and research grants to scientific institutions and to individual scientists.

The Institute also conducts educational activities, including the collection and dissemination of educational materials about these diseases, with emphasis on the prevention thereof, for health professionals and the lay public, and maintains continuing relationships with

institutions and professional associations and with international, national, and State and local officials, and voluntary agencies and organizations working in these areas.

For further information, call 301-496-2411.

National Library of Medicine

The Library, which serves as the Nation's chief medical information source, is authorized to provide medical library services and on-line bibliographic searching capabilities, such as MEDLINE, TOXLINE, and others, to public and private agencies and organizations, institutions, and individuals. It is responsible for the development and management of a Biomedical Communications Network, applying advanced technology to the improvement of biomedical communications, and operates a computer-based toxicology information system for the scientific community, industry, and other Federal agencies. In addition, the Library acquires and makes available for distribution audiovisual instructional material, and develops prototype audiovisual communication programs for the health educational community. Through grants and contracts, the Library administers programs of assistance to the Nation's medical libraries that include support of a Regional Medical Library network, research in the field of medical library science, establishment and improvement of the basic library resources, and supporting biomedical scientific publications of a nonprofit nature.

For further information, call 308-496-6308.

National Institute of Diabetes and Digestive and Kidney Diseases

The Institute conducts, fosters, and supports basic and clinical research into the causes, prevention, diagnosis, and treatment of the various metabolic and digestive diseases. It covers the broad areas of diabetes, blood, endocrine, and metabolic diseases; digestive diseases and nutrition; and kidney and urologic diseases, joined with the Artificial Kidney/Chronic Uremia Program, through research performed in its own

laboratories and clinics, research grants, individual and institutional research training awards, applied research and development programs through the contract mechanisms, field epidemiologic and clinical investigations studies on selected populations in the United States, and collection and dissemination of information on Institute programs.

For further information, call 301-496-5741.

National Institute of Allergy and Infectious Diseases

The Institute conducts and supports broadly based research and research training on the causes, characteristics, prevention, control, and treatment of a wide variety of diseases believed to be attributable to infectious agents, including bacteria, viruses, and parasites, to allergies, or to other deficiencies or disorders in the responses of the body's immune mechanisms. Among areas of special emphasis are: asthma and allergic disease, clinical immunology, including organ transplantation, venereal diseases, hepatitis, influenza and other viral respiratory infections, disease control measures, research and development, antiviral substances, and hospital-associated infections.

For further information, call 301-496-1521.

National Institute of Child Health and Human Development

The Institute conducts and supports biomedical and behavioral research on child health and maternal health; on problems of human development, with special reference to mental retardation; and on family structure, the dynamics of human population, and the reproductive process. Information related to these research findings is disseminated to other researchers, medical practitioners, and the general public to improve the health of children and their families.

For further information, call 301-496-3454.

National Institute on Deafness and Other Communication Disorders

The Institute conducts and supports research and training with respect to disorders of hearing and other communication processes, including diseases affecting

National Eye Institute The Institute conducts and supports fundamental studies on the eye and visual system, and on the causes, prevention, diagnosis, and treatment of visual disorders.

For further information, call 301-496-7425.

National Institute on Aging The Institute conducts and supports biomedical and behavioral research to increase the knowledge of the aging process and associated physical, psychological, and social factors, resulting from advanced age. Incontinence, menopause, susceptibility to diseases, and memory loss are among the areas of special concern.

For further information, call 301-496-5345.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

The Institute conducts and supports fundamental research in the major disease categories of arthritis and musculoskeletal and skin diseases through: research performed in its own laboratories and clinics, epidemiologic studies, research contracts and grants, and cooperative agreements to scientific institutions and to individuals. It supports training of manpower in fundamental sciences and clinical disciplines, conducts educational activities, including the collection and dissemination of health educational materials on these diseases, and coordinates with the other research institutes and with all Federal health programs relevant activities in the categorical diseases.

For further information, call 301-496-4353.

Clinical Center The Center is designed to bring scientists working in the Center's laboratories into close proximity with clinicians caring for patients, so that they may collaborate on problems of mutual concern. The research institutes select patients, referred to the National Institutes of Health by physicians throughout the United States and overseas, for clinical studies of specific diseases and disorders. A certain percent of the patients are "normal volunteers," healthy persons who provide an index of normal body functions against which to

measure the abnormal. Normal volunteers come under varied sponsorship, such as colleges, civic groups, and religious organizations.

For further information, call 301-496-3227.

Fogarty International Center The Center promotes discussion, study, and research on the development of science internationally as it relates to health and administers a number of international programs for advanced study in the health sciences.

For further information, call 301-496-4625.

National Center for Human Genome Research

The Center advises the Director of NIH and senior staff on all aspects of genomic analysis; coordinates the integration, review, and planning of genomic analysis research; formulates research goals and long-range plans with the guidance of the NIH Program Advisory Committee on Complex Genomes; serves as a focal point for coordination within NIH and will be the HHS point of contact for Federal interagency coordination, collaboration with industry and academia, and international cooperation; fosters, conducts, supports, and administers research and research training programs directed at promoting the growth and quality of research relating to mapping and sequencing of complex genomes through: (a) research grants, contracts, and cooperative agreements with institutions and individuals, (b) individual and institutional research training awards, (c) promotion of closer interaction with other bases of genomic analysis research, and (d) collection and dissemination of research findings in these areas. The Center develops plans for the centralized, systematic-targeted effort to create detailed maps of the genomes of organisms; sponsors scientific meetings and symposia to promote progress through information sharing; and fosters national and international information exchanges with industry and academia concerning research on complex genomes.

For further information, call 301-496-0844.

National Center for Nursing Research The Center fosters, conducts, supports, and administers research and research training programs aimed at promoting the growth and quality of research related to nursing and patient care and expanding the pool of experienced nurse researchers.

For further information, call 301-496-0523.

Division of Computer Research and Technology

The Division conducts an integrated research, developmental, and service program in computer-related physical and life sciences in support of Institute biomedical research programs.

For further information, call 301-496-5206.

National Center for Research Resources

The Center administers, fosters, and supports research for the development and support of various research resources needed on an institutional, regional, or national basis for health-related research. Programs are carried out through research grants and individual and institutional research training awards; cooperation and collaboration with organizations and institutions engaged in multicategorical research resource activities; and collection and dissemination of information on research and findings in these areas. The Center oversees a centralized program of intramural research resources through the planning, performance, and reporting of research projects.

For further information, call 301-496-5605.

Division of Research Grants

The Division provides staff support to the Office of the Director, National Institutes of Health, in the formulation of grant and award policies and procedures, central receipt of all Public Health Service applications for research and research training support, and makes initial referral to Service components.

For further information, call 301-496-7881.

hearing, balance, voice, speech, language, taste, and smell through a diversity of research performed in its own laboratories; a program of research grants, individual and institutional research training awards, career development awards, center grants, and contracts to public and private research institutions and organizations.

For further information, call 301-496-7243.

National Institute of Dental Research

The Institute supports and conducts clinical and laboratory research directed toward the ultimate eradication of tooth decay and of a broad array of oral-facial disorders.

For further information, call 301-496-6621.

National Institute of Environmental Health Sciences

The Institute, located in Research Triangle Park, NC, conducts and supports fundamental research concerned with defining, measuring, and understanding the effects of chemical, biological, and physical factors in the environment on the health and well-being of man.

For further information, call 919-541-3212 or (FTS) 8-629-3211.

National Institute of General Medical Sciences

The emphasis of the Institute's programs for support of research and research training is basic biomedical science. The activities range from cell biology to genetics to pharmacology and systemic response to trauma and anesthesia.

For further information, call 301-496-7714.

National Institute of Neurological Disorders and Stroke

The Institute conducts and supports fundamental and applied research on human neurological disorders such as Parkinson's disease, epilepsy, multiple sclerosis, muscular dystrophy, head and spinal cord injuries, and stroke. The Institute also conducts and supports research on the development and function of the normal brain and nervous system in order to better understand normal processes relating to disease states.

For further information, call 301-496-5751.

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February 4, 1991

OFFICE OF THE
DIRECTOR

Allan Bromley
Office of Science Technology Policy
The White House
Washington, D.C. 20500

Dear Allan:

I want to congratulate you on the FY 1992 science budgets. It is clear that you have succeeded in a heroic effort to shore up American science. I tried hard to get to see you before we went to press with our report to the AAAS Board. It is essential that what we do to advance the discussion of "how much science?" is supportive of your program. I hope we can support the effort to get the FY92 numbers through Congress.

Sincerely,



Leon M. Lederman

LML/kev