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FROM: BRUCK, Stephen D.: JOURNAL OF LONG TERM EFFECTS OF MEDICAL IMPLANTS

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 08/17/92

SUBJECT: HE IS FORWARDING A PREPRINT OF HIS EDITORIAL ENTITLED "IMPLANT RETRIEVAL, ANALYSIS, AND DATABASE: A CHALLENGE FOR THE MEDICAL DEVICES INDUSTRY".

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STAFF ASSIGNED: D.A. Henderson

ACTION REQUIRED: AS APPROPRIATE

STAFF ACTION: AS APPROPRIATE

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Stephen D. Bruck Associates, Inc.
Biomaterials and Medical Devices Consulting Group
P.O. Box 828
Rockville, MD 20848-0828
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Boca Raton, FL 33431

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August 17, 1992

The Honorable D. Allan Bromley
Assistant to the President
for Science and Technology
Old Executive Office Building, Room 360
17th Street and Pennsylvania Avenue, N.W.
Washington, D.C. 20506

Dear Dr. Bromley:

I am enclosing a preprint of my editorial entitled: "Implant Retrieval, Analysis, and Database: A Challenge for the Medical Devices Industry", that will appear in the Journal of Long-Term Effects of Medical Implants, volume 2, issue 2, 1992.

I believe that the message of my article, that is also shared by many members of our Editorial Board as well as other clinical and non-clinical experts, might be of interest to you.

I would be delighted to meet with you and/or members of your staff to discuss the matter in more detail.

I look forward to hearing from you.

Sincerely,

Stephen D. Bruck, M.D., Ph.D.
Editor-in-Chief

Encl.

PREPRINT

JOURNAL OF LONG-TERM EFFECTS OF MEDICAL IMPLANTS,
Volume 2, issue 2, 1992

Implant Retrieval, Analysis, and Database: A Challenge for the Medical Devices Industry

Stephen D. Bruck, Ph.D., Editor-in-Chief, Journal of Long-Term Effects of Medical Implants, c/o Biomaterials and Medical Devices Consulting Group, Stephen D. Bruck Associates, Inc.,
P.O. Box 828, Rockville, Maryland 20848-0828

ABSTRACT

Despite the widespread use of various medical implant devices since the 1960s, there has not been any systematic effort developed for implant retrieval, analysis, and data banking. Most medical implants fail prematurely because of selection of wrong materials, selection of wrong *in vitro* testing methods, inappropriate extrapolation to *in vivo* conditions, and/or ignorance of the state-of-art. Inasmuch as another federal effort is unlikely to deal effectively with these problems, it is proposed that the medical devices industry establish an independent Institute for Medical Implant Retrieval and Analysis, using a small percentage of profits gained from the sale of implants. In addition to carrying out in-house work, this Institute would support appropriate projects in selected academic institutions, with appropriate feedback to regulatory agencies internationally.

KEY WORDS: medical implants, medical implant retrieval, medical implant analysis, failure of medical implants, medical implants, biomaterials.

BACKGROUND

Since the enactment of the Medical Devices Amendment in 1976, there has been an explosive growth in the number and variety of medical devices and implants. Some good, some bad, and many unneeded (with the latter contributing to our devastating health-care costs). The vast majority of these were "grandfathered-in" by the broad interpretation of Regulation 510 (k) by the Food and Drug Administration (FDA). This Regulation provided de facto means to circumvent the premarket approval process by claiming that a device or implant was "substantially equivalent" to one marketed prior to 1976. The subsequent premature failures of some of these devices and implants led to the birth of the Safe Medical Devices Act of 1990 (1,2). Among others, The Act mandates the FDA to require manufacturers to conduct postmarket surveillance for any device that the manufacturer first introduced or delivered for introduction into interstate commerce after January 1, 1991, if the device is a permanent implant where failure may cause serious, adverse health consequences or death or is intended for a use in supporting or sustaining human life, or potentially presents a serious risk to human health.

Although the FDA has had 16 years since the enactment of the Medical Devices Amendment in 1976 (with numerous medical devices and implants used for over 35 years), there has not been any systematic effort developed for implant retrieval and analysis.

This was not the result of any lack of funds or personnel. The matter was simplistically ignored.

Components of medical devices and implants (materials) have been described, more often than not, in 510 (k) submissions to the FDA by their generic names and classifications (e.g., polyurethanes, silicones, polyesters, etc.) Often, inaccurate and wrong names are used even in the literature, such as "teflons" or "dacrons" or "carbons" (interchangeably used often for graphite, isotropic carbon, etc.), to describe materials. Without detailed and clear identification of all components of implants, any subsequent analyses of retrieved implants will yield misleading results or involve expenditures for chemical "detective" work that would exhaust the funds available for their intended purpose.

POTENTIAL PROBLEM AREAS

To overcome this barrier, the Safe Medical Devices Act of 1990 would have to be amended to require all manufacturers of implantable devices to fully disclose the compositions of materials with full qualitative and quantitative identification of additives in the materials. Materials used in current implants are not all that "new" despite the often appealing trade names coined to imply some new biological propensity to the material. For example, there are essentially two main classes of polyurethanes: ester or ether type ones (with either type being either aromatic or aliphatic).

Yet, there are numerous polyurethane products on the market that often differ only in some minor aspect from each other, including the additives and/or processing conditions. No useful data bases are possible unless one knows the exact composition of materials prior to their implantation in humans. Similarly, any effective implant retrieval and analyses would become highly complicated and may lead to wrong conclusions as to the causes of failure of implanted medical devices.

Another consideration is the safe handling of retrieved implants from the body (3). Uniform sterilization and preservation methods would have to be established and tested so that the physico-chemical, mechanical, and biological properties of retrieved implants do not change prior to analysis. Otherwise artifacts may be introduced that may negate the scientifically valid interpretations of failure modes.

Still another consideration is the possibility that therapeutic agents administered during the residence time of implants in the body could have affected and/or may have been taken up by the materials in the implanted devices. This possibility then requires that the medical history of the patients be known from whom the implants were retrieved.

Would another federal effort effectively deal with these problems? Unlikely. The FDA has had a rather poor track record since 1976

even in promulgating guidance documents to industry of what is required to assure the appropriate testing and evaluation of critical medical implants. It has neither the experience nor the in-house expertise to run an effective implant retrieval system. These exigencies and the current, well-staged publicity on breast implants following their introduction some 25 years earlier, does not indicate any lack of funding in the past but rather underlines the predominant effect of political considerations in relation to what is considered as "public health needs" in the medical devices area. Lack of sufficient expertise on the part of developers as well as regulators often leads to failures that could have been prevented.

MAIN CAUSES OF FAILURES

While some failures are inevitable, most implants fail prior to their intended service lives because one or more of the following: (1) selection of wrong materials; (2) selection of wrong <u>in vitro</u> testing methodologies; (3) inappropriate extrapolation to <u>in vivo</u> conditions and sometimes using the wrong animal species; (4) lack of acquisition of long-term data (where appropriate) for similar implants or materials; and (5) ignorance of the state-of-art.

EXAMPLES OF FAILURES DUE TO IGNORANCE

Ignorance of the state-of-art is represented by numerous examples. I will just list a few. The potential problems (rupture and gel-bleeding) with silicone gel implants and degradation of polyurethane-covered breast implants were simply due to already known, general scientific factors (thermodynamics and physical chemistry of polymers) in the literature dating back to the 1950s and hence were predictable. These include the predictable permeation of silicone fluids through silicone envelopes and the predictable hydrolysis of the ester-type polyurethane used in the coating of the silicone envelopes. Similarly, the degradation of PROPLAST (a carbon-fiber reinforced polytetrafluoroethylene copolymer) (4), as temporomandibular joint prostheses was predictable based on work done on composites for biomedical publications in the 1970s under federal contracts. This product was not properly evaluated, and warranted extrapolations were made to <u>in vivo</u> conditions from scant <u>in vitro</u> data. Yet, this product was approved as being "substantially equivalent" (510 (k) Regulation). It has been recently removed from the market by the FDA following disastrous clinical consequences (5). Also, approved was the GARREN-EDWARDS GASTRIC BUBBLE made from ester-type polyurethane that quite predictably hydrolyzed in the highly acidic environment of the stomach within a short time (6). Information was readily available on the stability of such materials as early as the 1960s in various journal articles (7, 8) and the pH values

in the stomach were certainly known for over 100 years. The performance of polyurethanes in the envisioned, widespread use of electrically driven, "permanent" artificial hearts is likewise predictable: they will degrade with long-term (years) use in the body with catastrophic consequences. However, the date for the widespread, clinical uses of such devices has been steadily pushed upwards since the 1960s and currently promised for the early 21st Century (9). Presumably by then some new magic, fully hemocompatible, non-immunogenic, non-carcinogenic, and long-lasting (minimum of 10 years in the body) material might be discovered that can function reliably without the need for anticoagulants and without the need for other pharmaceutical agents in the human cardiovascular system.

A CHALLENGE FOR INDUSTRY: ESTABLISHMENT OF AN INSTITUTE FOR MEDICAL IMPLANT RETRIEVAL AND ANALYSIS

Manufacturers are obviously interested in improving their products. They also want to minimize the possibility of litigations. In view of the above, it is proposed that industry establish an independent Institute for Medical Implant Retrieval and Analysis to be funded from a small percentage of the profits gained from the sale of implants. There is no need for using the taxpayers' moneys or to establish another federal "white elephant" that could easily grow into a mammoth and result in ineffective regulations. This

Institute would be administered by a Board of Directors (on a rotating basis) and would use outside consultants, as needed. The Institute would effectively collaborate with appropriate clinicians in the medical profession. In addition to in-house efforts, the Institute would support also work in academic centers, medical schools, and in our already existing National Laboratories, thereby attaining the combined goals of product improvement, innovations, effective promotion of industry-academic interchange, and utilization of existing resources in the interest of public health. The activities of this Institute will be of particular benefit to small firms which do not have adequate resources. Furthermore, other nations will be expected to establish similar institutions, thus facilitating international cooperation. The FDA would benefit by such an enterprise with the availability of relevant information that would provide more scientifically valid decisions and assure an enthusiastic industrial involvement on a non-coercive basis.

In summary, good failure analyses of retrieved, implanted medical devices and the establishment of reliable data banks are desirable. However, unless we are ready to nationalize the medical devices industry and health-care system in the U.S.A., let us simplify matters by stimulating socially responsible, private initiatives without the reliance on still another federal "white elephant" with its predictable exponential funding appetite from the taxpayers and all too often, bureaucratic inertia.

REFERENCES

1. Public Law 101-629, 101st Congress, 1990.

2. Bruck, S.D. and Silver, F.H., The Safe Medical Devices Act of 1990 (Editorial), J. Long-Term Effects of Medical Implants, 1991, 1 (2): 121-126.

3. Bruck, S.D., Identification of biodegradation products of medical implants in adjacent tissues: an overview and recommendations, J. Long-Term Effects of Medical Implants, 1992, 1 (4): 357-364.

4. Homsy, C.A., Proplast: chemical and biological considerations. In: Rubin, L. R., Biomaterials in Reconstructive Surgery, St. Louis: C. V. Mosby, 1983; 91-101.

5. Anon., Devices & Diagnostics Letter, 1992, 19 (23):5.

6. Dillon, J.G. and Hughes, M.K., Degradation of five polyurethane gastric bubbles following in vivo use: SEC, ATR-IR and DSC studies, Biomaterials, 1992, 13 (4): 240-248.

7. Ossefort, Z. T. and Testroet, F. B., Hydrolytic stability of urethane elastomers, Rubber Chem. Technol., 1966, 39:1308-1327.

8. Pentz, W. J. and Krawiec, R. G., Hydrolytic stabilty of polyurethane elastomers, Rubber Age, 1975, 107:39-43.

9. Pierce, W. S., The artificial heart: paths, progress and patience, Artif. Organs, 1992, 16 (3): 314-326.

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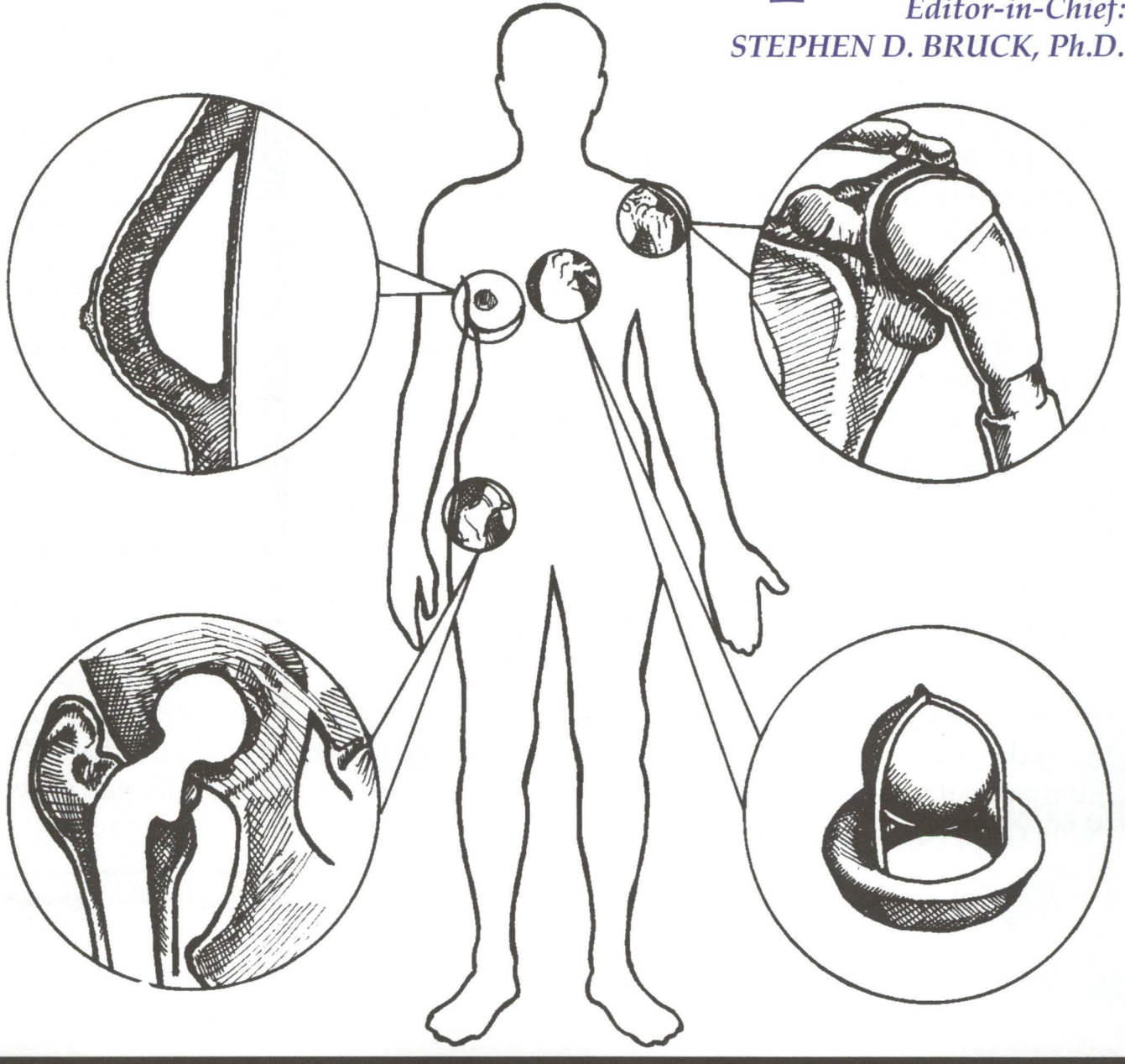

Aim & Scope...

The ability to predict the long-term *in vivo* performance of medical implants is of vital interest. The extrapolation of *in vitro* data to the *in vivo* environment remains largely unproven. Among the major difficulties are our limited ability to simulate the complexities of the biological milieu, the current lack of reliable computer modeling of *in vivo* performance characteristics of implants, and difficulties in evaluating the synergistic contributions of materials, design features, and therapeutic drug regimens.

The aims of this Journal are the better understanding of the mechanisms of failure of pre-clinically tested medical implants during long-term *in vivo* service life both in appropriate animal models and in humans, and establishing an effective linkage between pre-clinical and clinical studies. Of particular interest are original, critical analyses of data of retrieved implants, interpretive discussions of data based on invasive and non-invasive procedures, and computer modeling of *in vivo* performance. A special section will be devoted to articles on health-care technology assessment involving implants, and their social impact and economic consequences. The Journal will also publish guest editorials and letters-to-the-editor. All papers will be subject to peer reviews by at least two referees.

The Journal will be of benefit to manufacturers, health-care providers, researchers, and patients, and will have wide appeal to clinicians, scientists, and engineers working in the field of medical implants. A distinguished international Editorial Advisory Board has been appointed, representing the clinical and non-clinical disciplines.

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TO: DR. D.A. BROMLEY

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SUBJECT: LETTER REQUESTING SIGNATURE OF BILL S.544.

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American Heart Association
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August 18, 1992

The Honorable George Bush
The White House
Washington, D.C. 20500

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Dear Mr. President:

On behalf of the 3.5 million American Heart Association volunteers, I respectfully request that you sign into law, S. 544 the "Animal Enterprise Act of 1992." S. 544 represents a carefully crafted, widely supported compromise measure that has been worked on for more than four years by a broad range of organizations representing biomedical research, education, agriculture, animal exhibitions, humane and animal protection groups, the ACLU and federal agencies.

The American Heart Association is dedicated to the reduction of disability and death from cardiovascular diseases and stroke. Despite progress in this area, cardiovascular diseases remain the number one killer in the United States. The decline in the age-adjusted death rate from heart attack and stroke is largely related to changes in lifestyles and development of methods of treatment, many of which are based on animal experimentation. There is no satisfactory way besides the animal model to reproduce the extraordinary complexity of the human cardiovascular system. Development of new knowledge, testing of new drugs, and refinement of new devices and operations that affect the cardiovascular system require animal experimentation.

During the past ten years research facilities have been under attack by radical animal rights extremists who seek to abolish all animal research. These attacks have included terrorist-type acts such as arson, break-ins, bomb threats, death threats, theft of animals and laboratory equipment, and vandalism and destruction of property, including irreplaceable research records and data. S. 544 would provide criminal penalties for such violent acts against both farm and research facilities. With these violent acts increasing in both number and severity, the research community believes that it is imperative for the United States to protect our nation's animal facilities.

Federal protection for animal facilities is not being sought to stop necessary debate or to stifle opinion. This legislation does not supersede state or federal whistleblower protection laws, nor does it interfere with legitimate investigations or media activities. Only those acts committed with the intention to physically disrupt or damage an animal facility would be prohibited by S. 544.

I strongly urge you to sign S. 544, the "Animal Enterprise Act of 1992." Thank you.

Respectfully,

Edward S. Cooper

Edward S. Cooper, M.D.
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cc: Dan Quayle
D. Allan Bromley

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Senior Vice President Scientific Affairs
Rodman D. Starke, M.D.

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TYPE: INFORMATION DOCUMENT NUMBER: 9202742
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS

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FROM: ROSE, TIM: NATIONAL PORK PRODUCERS COUNCIL

TO: PRESIDENT BUSH

DATE OF
CORRESPONDENCE: 08/17/92

SUBJECT: REQUEST THAT PRESIDENT BUSH SIGN S.544, "THE ANIMAL ENTERPRISE PROTECTION ACT OF 1992."

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

****

SENDER'S DUE DATE:

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COPIES TO: D. Allan Bromley
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2742

NATIONAL PORK
Producers Council

WASHINGTON OFFICE
501 SCHOOL STREET, S.W., SUITE 400, WASHINGTON, D.C. 20024
PHONE 202-554-3600, FAX 202-554-3602

RECEIVED
92 AUG 19 P12:51
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August 17, 1992

The Honorable George Bush
President of the United States
The White House
1600 Pennsylvania Avenue
Washington, D.C. 20500

Dear President:

The National Pork Producers Council which represents nearly 100,000 pork producers across the United States, requests that you sign S. 544, "The Animal Enterprise Protection Act of 1992." Pork producers have listed this measure as a top legislative priority for more than two years.

The Act helps foster a healthy environment for the production of food as well as important research for humans and animals alike. Your approval of this bill would help to discourage radical activists who commit acts of violence against farmers and researchers. There are more than 100 recorded incidents of such criminal activities nationwide in the last 10 years.

Therefore, a national coalition of groups, ranging from livestock producers to biomedical researchers to universities, joined the National Pork Producers Council in endorsing S. 544. This Act also received widespread support in Congress as it had 264 cosponsors in the House of Representatives and passed by unanimous consent in the Senate.

The pork industry is dedicated to the humane care of animals, which is why we spend more than $100,000 annually on scientific swine care research. Furthermore, the industry has developed many informational materials that encourage proper animal care. The Animal Enterprise Protection Act of 1992 will help ensure that pork producers can go about their jobs of providing good animal care that results in valuable protein for the American public.

Sincerely,

Tim Rose
President

TYPE: INFORMATION DOCUMENT NUMBER: 9202482
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS
****

FROM: SCHROTE, JOHN: US DEPARTMENT OF THE INTERIOR

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 08/17/92

SUBJECT: LETTER REGARDING ISSUES RAISED IN A JULY 6, 1992 LETTER REGARDING SCIENTISTS USING GOVERNMENT RESOURCES TO PRESS FOR THEIR PERSONAL AGENDA.

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

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SENDER'S DUE DATE:

OSTP DUE DATE:

STAFF DUE DATE

DATE COMPLETED:

DATE COMPLETED/DEPT:

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COPIES TO: D. Allan Bromley

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FILE: P-LIFE SCIENCES-ETHICS

CENTRAL FILES:

2482

United States Department of the Interior

OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20240

AUG 17 1992

Honorable D. Allan Bromley
Assistant to the President for
Science and Technology
The White House
OEOB, Room 358
Washington, DC 20506

Dear Dr. Bromley:

Thank you for looking into the issues raised in our July 6, 1992, letter regarding scientists using Government resources to press for their personal agenda. It was gracious of you to take the time to respond.

As noted in the letter, our concerns are with the news article and with the degree to which the article was relevant and accurate.

Certainly, we concur with the importance of free and open discussion of methodology and data. However, we do question the conclusion of one individual, particularly when the data and rationale have not been "scrubbed" by the scientific community. You noted the data was submitted to this Department on June 22, almost a week after my letter to you and 11 days after the article appeared. It would appear that Dr. Tucker made little or no effort to confirm his conclusion with on-the-ground observation from the land management agencies.

The article attributed direct quotes to Dr. Tucker and noted that he made his pictures available because he thought the comparison was relevant to the international debate. The international debate at that time was going on in Rio.

The concern of this Department is that there are times when public policy is being advocated in the name of science when, in fact, the science, if any, is political science (which is not, of course, a science).

Thank you for hearing us out.

Sincerely,

JOHN E. SCHROTE
Assistant Secretary
Policy, Management and Budget

"Document Control for Division of Life Sciences"

TYPE: ACTION DOCUMENT NUMBER: 9202458
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

****

FROM: BORDER, Wayne A.: UNIVERSITY OF UTAH

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 08/17/92

SUBJECT: HE IS WRITING TO DR. BROMLEY REGARDING HIS ATTEMPTS TO SECURE FUNDING FOR HIS RESEARCH ON TGF-B.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED: D.A. Henderson

ACTION REQUIRED: AS/IF NECESSARY

STAFF ACTION: AS/IF NECESSARY

****

SENDER'S DUE DATE:

OSTP DUE DATE: 09/09/92 STAFF DUE DATE 09/04/92
DATE COMPLETED: DATE COMPLETED/DEPT: 08/31/92

****

COPIES TO: D. Allan Bromley

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WHITE HOUSE TRACKING #:

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OSTP RECEIVED: 08/26/92 DEPT RECEIVED: 08/27/92
FILE: P-LIFE SCIENCES

CENTRAL FILES:

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

August 31, 1992

Dear Dr. Border:

Dr. Bromley asked that I reply to your letter of August 17 pertaining to transforming growth factor and decorin.

I had been aware of your work and was very happy to have the opportunity to see the pre-publication papers to appear in Nature and the Proceedings of the Academy. I share your view that your findings offer promise for dealing with a variety of different diseases extending well beyond the nephropathies. Identifying inhibitors that can be administered therapeutically will be a challenge I am sure.

Thank you for sharing this information with us. I wish you well in your efforts to secure NIH funding.

Sincerely yours,

D.A. Henderson, M.D., M.P.H.
Associate Director for Life Sciences

Wayne A. Border, M.D.
Professor of Medicine
Chief, Division of Nephrology and
Hypertension
The University of Utah
Health Sciences Center
Salt Lake City, Utah 84132

2458

THE UNIVERSITY OF UTAH

RECEIVED

92 AUG 26 A10 : 44

OSTP
MAIL ROOM

August 17, 1992

Dr. D. Allan Bromley
Assistant to the President
Science and Technology
Director, Science and Technology Policy
White House, Washington, DC 20500

Dear Dr. Bromley:

Senator Jake Garn and Mr. Stephen Kohashi of the Senate Appropriations Committee suggested that I write to tell you of our exciting discoveries that transforming growth factor-ß (TGF-ß) is a cause of kidney scarring in diabetes and glomerulonephritis and that decorin, a natural inhibitor of TGF-ß, may be used as a novel therapy to prevent kidney failure in humans with these disorders. There is also a growing body of evidence that TGF-ß may be the cause of fibrosis and scarring in a number of other human diseases. Our work on TGF-ß and disease is reviewed in the lead article in the July issue of the Journal of Clinical Investigation and is illustrated on the Journal's cover. The original research papers describing the work in diabetic kidney disease and the use of decorin will, respectively, be published in Nature and the Proceedings of the National Academy of Sciences. I have enclosed copies of the new articles as well as those of two key earlier studies.

The reason for telling you about our work on TGF-ß, decorin and scarring is that it offers hope that a treatment can be developed for a number of chronic human diseases involving kidney, lung, liver, etc. for which currently there are few or no effective therapies. The cost to the federal government of providing health care to patients suffering from these diseases must be enormous. It is known that the annual cost of kidney dialysis and transplantation alone is nearly five billion dollars.

One example of these chronic disorders in which organ function is destroyed by scarring or fibrosis is diabetic kidney disease. Almost everyone in America knows of someone who has developed diabetic kidney disease and kidney failure. Despite the universal availability of insulin, diabetic kidney disease has increased at an alarming rate and is now the most common cause of kidney failure. This suggests a major deficiency in understanding of the pathogenesis of this disease. I believe that our research provides an explanation. It appears that the kidney in diabetes expresses TGF-ß which causes the deposition of extracellular matrix (scarring) in a manner similar to a healing wound. In our review on TGF-ß and disease we provide evidence that the same TGF-ß-mediated wound healing process underlies analogous pathologies in many other organs, possibly including some of the complications of AIDS.

Division of Nephrology

Health Sciences Center
Salt Lake City, Utah 84132
(801) 581-6709
FAX (801) 581-4343

August 17, 1992

In our most recent work, we have shown that decorin, a human protein that is a natural inhibitor of TGF-ß, can block kidney scarring in an experimental model of glomerulonephritis. We plan to test decorin in other models of tissue scarring including diabetic kidney and eye disease. Whether decorin will be the best inhibitor of TGF-ß for use as a human drug is unclear; but, it is likely that some TGF-ß inhibitor will become an important future therapy.

Dr. Bromley, I feel that increased federal awareness, recognition and support of TGF-ß/scarring research would accelerate the potential development of important new therapies for a number of human diseases. These therapies might provide huge federal savings in health care. Surprisingly, despite the clearly innovative nature of this research, I have had difficulty getting NIH funding for the studies on glomerulonephritis, which are central to the entire research effort. In any event I plan to submit another grant application shortly.

Thank you for your interest. I would be delighted to provide additional information or answer any questions that you might have.

Sincerely,

Wayne A. Border, M.D.
Professor of Medicine
Chief, Division of Nephrology and Hypertension

/mti

Elevated Expression of Transforming Growth Factor-β and Proteoglycan Production in Experimental Glomerulonephritis

Possible Role in Expansion of the Mesangial Extracellular Matrix

Seiya Okuda, Lucia R. Languino,* Erkki Ruoslahti,* and Wayne A. Border
*Division of Nephrology, University of Utah School of Medicine, Salt Lake City, Utah 84132; and *Cancer Research Center, La Jolla Cancer Research Foundation, La Jolla, California 92037*

Abstract

Glomerular accumulation of extracellular matrix is a prominent feature of progressive glomerulonephritis. Previously, we have shown that transforming growth factor-β (TGF-β) is unique among growth factors in regulating the production of the proteoglycans biglycan and decorin by glomerular mesangial cells in vitro. We now provide evidence of an elevated expression of TGF-β, proteoglycans, and fibronectin in glomerulonephritis induced in rats by injection of anti-thymocyte serum (ATS). Glomeruli were cultured from rat kidneys at 1, 4, 7, 14, and 28 d after ATS administration. Increased proteoglycan synthesis was detected beginning on day 4, which peaked at a 4,900% increase compared with control on day 7, and returned toward control levels by day 28. The increased proteoglycan synthesis by cultured nephritic glomeruli, as well as that of fibronectin, were greatly reduced by addition of antiserum raised against a synthetic peptide from TGF-β. Conditioned media from ATS glomerular cultures, when added to normal cultured mesangial cells, induced elevated proteoglycan synthesis that also peaked on day 7 and that mimicked the response to added exogenous TGF-β. The stimulatory activity of the conditioned media was blocked by addition of TGF-β antiserum. Prior addition of the immunizing peptide to the antiserum abolished the blocking effect. The main induced proteoglycans were identified as biglycan and decorin by immunoprecipitation with antiserum made against synthetic peptides from the proteoglycan core proteins. Glomerular histology showed mesangial matrix expansion in a time course that roughly paralleled both the elevated proteoglycan synthesis by the ATS glomeruli and the ability of the conditioned media from these glomeruli to induce proteoglycan synthesis. At the same time there was an increased expression of TGF-β mRNA and TGF-β protein in the glomeruli. These results suggest a central role for TGF-β in the accumulation of pathological extracellular matrix in glomerulonephritis. (*J. Clin. Invest.* 1990. 86:453–462.) Key words: extracellular matrix • glomerulonephritis • growth factor • kidney disease • mesangium • transforming growth factor-β

A preliminary report of this work was presented at the annual meeting of the American Society of Nephrology, Washington, DC, December 1989.

Address reprint requests to Dr. Border, Division of Nephrology, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132.

Received for publication 15 August 1989 and in revised form 27 March 1990

J. Clin. Invest.
© The American Society for Clinical Investigation, Inc.
0021-9738/90/08/0453/10 $2.00
Volume 86, August 1990, 453–462

Introduction

Accumulation of glomerular extracellular matrix and thickening of the glomerular basement membrane are important features of glomerulonephritis that progresses to end-stage renal disease and uremia (1). Although a variety of immunologic, hemodynamic, and toxic factors have been used to induce glomerular injury experimentally, we believe that none of these factors has been shown to directly influence synthesis or degradation of extracellular matrix components (2). Thus it seems likely that there is another intervening process between acute injury and buildup of glomerular extracellular matrix. Recently, transforming growth factor-β (TGF-β)[1] has been shown to have widespread effects on extracellular matrix (3, 4).

TGF-β is a multifunctional regulatory protein that can either inhibit or stimulate cellular proliferation (4, 5). There is now growing evidence that some of TGF-β's multiple actions (3) are mediated through regulatory effects on: (*a*) extracellular matrix synthesis (6–8), (*b*) enzymes that degrade extracellular matrix (9, 10), and (*c*) the expression of extracellular matrix receptors on cells (11).

The kidney is a prime target for the actions of a growth factor like TGF-β because the structure and filtration properties of the glomerulus are largely determined by the extracellular matrix composition of the mesangium and glomerular basement membrane (12). TGF-β has been isolated from bovine kidney (13) and rat kidney fibroblasts (14). Murine glomerular cells (15) have been shown, as has nearly every cell line (16), to possess TGF-β receptors. Indeed, we have found that TGF-β has marked effects on the extracellular matrix production by cultured mesangial cells (17). Its principal action is to increase the synthesis of two chondroitin/dermatan sulfate proteoglycans, biglycan and decorin, and it also stimulates the deposition of fibronectin onto the mesangial cell surface. Other growth factors implicated in glomerulonephritis, interleukin-1 (IL-1), platelet-derived growth factor (PDGF), and tumor necrosis factor (TNF) showed no significant effect on extracellular matrix production in that study.

In this report we have utilized a rat model of glomerulonephritis induced by specific immunologic injury to the mesangial cell to show that this disease process is accompanied by a marked increase in the expression of TGF-β and the proteoglycans known to be induced by it in cultured mesangial cells. The increased synthesis of proteoglycans, a marker of TGF-β activity, and fibronectin, a major matrix glycoprotein, by nephritic glomeruli in culture is dramatically reduced by addition of an antiserum to TGF-β. These results suggest that

1. *Abbreviations used in this paper:* ATS, anti-thymocyte serum; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor.

Reprinted from Nature, Vol. 346, No. 6282, pp. 371–374, 26th July, 1990
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Suppression of experimental glomerulonephritis by antiserum against transforming growth factor β1

Wayne A. Border*, Seiya Okuda*, Lucia R. Languino†, Michael B. Sporn‡ & Erkki Ruoslahti†

* Division of Nephrology, University of Utah School of Medicine, Salt Lake City, Utah 84132, USA
† Cancer Research Center, La Jolla Cancer Research Foundation, 10901 N. Torrey Pines Road, La Jolla, California 92037, USA
‡ Laboratory of Chemoprevention, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA

GLOMERULONEPHRITIS is an inflammation of the kidney characterized by the accumulation of extracellular matrix within the damaged glomeruli[1–4], impaired filtration and proteinuria. In its progressive form, the disease destroys kidney function leading to uraemia and death, unless dialysis therapy or kidney transplantation is available. The pathogenesis of glomerulonephritis is incompletely understood, but the eliciting factor is thought often to be an immunological injury to mesangial and/or other resident cells in the glomeruli[5,6]. We have used an animal model of acute mesangial proliferative glomerulonephritis[7,8] to show that this disease is associated with increased production and activity of transforming growth factor β1 (TGF-β1)[9], an inducer of extracellular matrix production[10–17]. Here we report that administration of anti-TGF-β1 at the time of induction of the glomerular disease suppresses the increased production of extracellular matrix and dramatically attenuates histological manifestations of the disease. These results provide direct evidence for a causal role of TGF-β1 in the pathogenesis of the experimental disease and suggest a new approach to the therapy of glomerulonephritis.

Kidney International, Vol. 41 (1992), pp. 566–570

Antagonists of transforming growth factor-β: A novel approach to treatment of glomerulonephritis and prevention of glomerulosclerosis

WAYNE A. BORDER, NANCY A. NOBLE, TATSUO YAMAMOTO, SUGURU TOMOOKA, and SHOJI KAGAMI

Division of Nephrology, University of Utah School of Medicine, Salt Lake City, Utah, USA

Transforming growth factor-β (TGF-β) is the prototype of a polypeptide regulatory factor [1]. TGF-β exists in mammals in three isoforms, TGF-β1, 2 and 3 and acts on virtually every mammalian cell type regulating an array of cellular functions. TGF-β is multifunctional in that depending on the state or context of the cell, TGF-β can either stimulate or inhibit the same process [2]. One of the most important properties of TGF-β is its widespread effects on extracellular matrix. Most cells in the body, including glomerular mesangial cells, are surrounded by a complex superstructure of interacting glycoproteins, collagens and proteoglycans called extracellular matrix [3]. The glomerular basement membrane represents a second form of specialized extracellular matrix in the glomerulus. Both glomerular matrices are important in determining the biophysical properties of permeability and filtration. All cells possess specific matrix surface receptors through which they adhere to the matrix [4]. Cellular attachment to the matrix allows cells to grow, divide, differentiate, secrete products, move and form specialized tissues. TGF-β influences all of these cellular functions through its known actions to: 1) stimulate the production of extracellular matrix molecules; 2) inhibit enzymes that degrade matrix; and 3) increase the expression and adhesion phenotype of matrix receptors [1]. Collectively, TGF-β acts to enhance accumulation of extracellular matrix which is highly beneficial in a process such as wound repair, but deleterious when it occurs in the glomerulus in glomerulonephritis or diabetic nephropathy [5].

Recent evidence from our laboratory suggests that there are striking similarities between the role of TGF-β as a master regulator of wound repair, and the involvement of TGF-β in experimental glomerulonephritis (Fig. 1). The result of the action of TGF-β in wound repair in the skin is the formation of a scar. In the glomerulus, the same process can lead to sclerosis. Thus glomerulosclerosis can be viewed as the "dark side" of TGF-β and wound repair. This logic suggests a dual role for therapy. In some cases additional TGF-β is beneficial (wound repair) and in others, antagonism of TGF-β (glomerulosclerosis) is required [5].

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The known actions of TGF-β in wound repair are depicted in Figure 2. Most important is the recognized ability of TGF-β to initiate and then terminate the repair process. Failure to terminate the action of TGF-β in the glomerulus would set the stage for progressive glomerulosclerosis. Evidence for the involvement of TGF-β in experimental glomerulonephritis is as follows.

We chose a model of acute mesangial proliferative glomerulonephritis because mesangial proliferation and matrix expansion are among the most frequent changes seen in human glomerulonephritis [6]. Furthermore, expansion of the mesangial matrix in human diabetic nephropathy has been shown to be the central pathological change underlying the development of proteinuria, hypertension and decreased filtration [7]. Administration of anti-thymocyte serum to rats had previously been shown to produce a dose and complement-dependent selective injury to mesangial cells without affecting glomerular endothelial or epithelial cells. This immunological injury would be the equivalent of mechanical wounding in the skin. This model is particularly powerful because nephritic glomeruli can be acutely isolated from the kidney, placed in tissue culture, and labeled with isotopes to measure their biosynthetic products [8]. In earlier studies we had shown that TGF-β is unique among growth factors in stimulating cultured mesangial [9] and glomerular epithelial cells [10] to strikingly increase the production of two chondroitin/dermatan sulfate proteoglycans, biglycan and decorin. These two proteoglycans are now recognized as markers of TGF-β activity. In addition, TGF-β strongly induced epithelial cells and normal glomeruli to produce the major matrix glycoprotein, fibronectin.

Our results showed that by day 4 of disease there was a clear pattern of changes indicating the strong expression of TGF-β within the glomeruli [8]. Biglycan and decorin production by the nephritic glomeruli immediately increased and reached a 49-fold peak on day 7. Following the increase in glomerular proteoglycan production there was histological and ultrastructural evidence of enhanced accumulation of mesangial matrix which increased on day 7 and reached a peak on day 14. Due to the lysis of a portion of the mesangial cells by the anti-thymocyte serum, there was an initial period of glomerular hypocellularity, but by day 4 cellularity was normal due to influx of monocytes/

CONFIDENTIAL

NATURE: IN PRESS

DECORIN, A NATURAL INHIBITOR OF TRANSFORMING GROWTH FACTOR-ß, PROTECTS AGAINST SCARRING IN EXPERIMENTAL KIDNEY DISEASE

Wayne A. Border[1*], Nancy A. Noble[1], Tatsuo Yamamoto[1], John R. Harper[2], Yu Yamaguchi[3], Michael D. Pierschbacher[2,3] and Erkki Ruoslahti[3]

[1]Division of Nephrology, University of Utah School of Medicine, Salt Lake City, Utah 84132,

[2]Telios Pharmaceuticals, Inc., San Diego, California 92121

[3]Cancer Research Center, La Jolla Cancer Research Foundation, La Jolla, California, 92037

*Corresponding Author

CONFIDENTIAL

PROC. NATL. ACAD. SCI., USA: IN PRESS

EXPRESSION OF TRANSFORMING GROWTH FACTOR-ß IS ELEVATED IN HUMAN AND EXPERIMENTAL DIABETIC NEPHROPATHY

Key Terms: (Diabetes mellitus/ Kidney disease/ Extracellular matrix)

Tatsuo Yamamoto*

Takamichi Nakamura*

Nancy A. Noble*

Erkki Ruoslahti+

Wayne A. Border*≠

Abbreviations: TGF-ß, Transforming growth factor-ß

Fibronectin EDA+, Fibronectin extra domain A positive

GAPDH, Glyceraldehyde-3-phosphate dehydrogenase

*Division of Nephrology, University of Utah School of Medicine, Salt Lake City, Utah 84132; and +Cancer Research Center, La Jolla Cancer Research Foundation, La Jolla, California, 92037

≠To whom reprint requests should be addressed.

Transforming Growth Factor-β in Disease: The Dark Side of Tissue Repair

Wayne A. Border* and Erkki Ruoslahti‡
**Division of Nephrology, University of Utah School of Medicine, Salt Lake City, Utah 84132; and* ‡*Cancer Research Center, La Jolla Cancer Research Foundation, La Jolla, California 92037*

Introduction

Inflammatory, immune, and tissue repair responses protect us against a hostile and dangerous environment. However, these responses sometimes fail, mistarget, or overshoot and harm what they were meant to protect. For example, prostaglandins are important proinflammatory mediators that can also cause unwanted, painful reactions. As a result, we spend a part of our lives taking aspirin and other inhibitors of prostaglandin synthesis. The theme we would like to develop in this review is that, while a growing body of evidence implicates transforming growth factor-β (TGF-β)[1] as a cytokine vital to tissue repair, it also is one whose excessive action may be responsible for the tissue damage caused by scarring in many serious diseases. We propose that the pathological consequences of the action of TGF-β be termed the "dark side" of tissue repair. Inhibitors of TGF-β may be important future drugs in controlling this condition.

TGF-β: basic biology

TGF-β, a multifunctional cytokine, plays an important role in embryonal development and in regulating repair and regeneration following tissue injury (1–3). It consists of a family of three isoforms, TGF-β1, 2, and 3, that are structurally and functionally closely related to one another. The TGF-βs are members of a superfamily of cytokines that includes other regulators of differentiation and tissue repair such as activin, Müllerian inhibitory substance, and bone morphogenetic proteins (4). In their active form, all of these substances are dimers of a 12-kD polypeptide that arises from a larger precursor through proteolytic processing.

Multiple events involving TGF-β take place in tissue repair after injury. Platelets contain high concentrations of TGF-β and upon degranulation at a site of injury release TGF-β into the surrounding tissue (5). TGF-β then initiates a complex sequence of events that promotes healing including: chemoattraction of monocytes and leukocytes (6–8); induction of angiogenesis (9); and control of the production of cytokines and other inflammatory mediators (10–12).

Address correspondence to Wayne A. Border, M.D., Division of Nephrology, University of Utah School of Medicine, Salt Lake City, UT 84132, or to Erkki Ruoslahti, M.D., Cancer Research Center, La Jolla Cancer Research Foundation, La Jolla, CA 92037.

Received for publication 29 April 1992.

1. *Abbreviation used in this paper:* TGF-β, transforming growth factor-β.

J. Clin. Invest.
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0021-9738/92/07/0001/07 $2.00
Volume 90, July 1992, 1–7

Two additional features of the TGF-β response in injury may be the most important for the topic of this review: autoinduction of TGF-β production (13) and induction by TGF-β of increased deposition of extracellular matrix (9, 14, 15). TGF-β stimulates the synthesis of individual matrix components including fibronectin, in particular one of its variant forms, as well as tenascin, collagens, and proteoglycans (9, 16–20). It simultaneously blocks matrix degradation by decreasing the synthesis of proteases and increasing the levels of protease inhibitors (21, 22). TGF-β increases the expression of integrins and changes their relative proportions on the surface of cells in a manner that could facilitate adhesion to matrix (23). All these events can be beneficial in tissue repair. However, the dark side to the TGF-β effects is that the TGF-β-induced deposition of extracellular matrix at a site of tissue injury can lead to scarring and fibrosis. Furthermore, the ability of TGF-β to induce its own production may be the key to development of the scarring and fibrosis into chronic, progressive conditions that will in time obliterate the tissue structure.

TGF-β in kidney disease

Studies in a model of acute mesangial proliferative glomerulonephritis induced by injecting rats with antithymocyte serum show that production of TGF-β underlies the accumulation of glomerular extracellular matrix in this disease. The injured glomeruli express more TGF-β mRNA, synthesize more TGF-β protein, and produce many-fold more fibronectin and proteoglycans than do normal glomeruli (24). Simultaneous with increased matrix production is a striking decrease in plasminogen activator activity and a parallel increase in production and deposition of plasminogen activator inhibitor-1 in the nephritic glomeruli (Tomooka, S., W. A. Border, B. C. Marshall, and N. A. Noble, manuscript submitted for publication). The plasminogen/plasmin system is thought to play an important role in the normal degradation and turnover of matrix (25, 26). Thus both increased production and decreased removal are equally likely to contribute to the accumulation of pathological matrix in the disease. Fig. 1 illustrates the induction of TGF-β1 mRNA in the glomeruli of the nephritic kidney.

Injection of an antiserum capable of neutralizing the activity of TGF-β into the nephritic rats suppresses the production of matrix components by the glomeruli and prevents the buildup of mesangial matrix (27). Two of the proteoglycans induced by TGF-β in the glomerulonephritis model, decorin and biglycan, are inhibitors of TGF-β (28); their elevated expression under the influence of TGF-β may be not only a reflection of increased extracellular matrix production, but also a response to limit further activity of TGF-β. We have taken advantage of the ability of decorin to suppress TGF-β activity and have found that injections of decorin can also suppress the glomerulonephritic disease in the rats (Border, W. A., N. A.

"Document Control"

TYPE: INFORMATION DOCUMENT NUMBER: 9202753
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS
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FROM: KRAUT, ALAN G.: AMERICAN PSYCHOLOGICAL SOCIETY

TO: PRESIDENT BUSH

DATE OF
CORRESPONDENCE: 08/14/92

SUBJECT: A REQUEST URGING THE PRESIDENT TO SIGN INTO LAW S.544, THE "ANIMAL ENTERPRISE ACT OF 1992".

****
DIRECTORATE ASSIGNED: STAFF ASSIGNED:

ACTION REQUIRED: STAFF ACTION:

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SENDER'S DUE DATE:
OSTP DUE DATE: STAFF DUE DATE
DATE COMPLETED: DATE COMPLETED/DEPT:

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COPIES TO: LIFE SCIENCES
D. Allan Bromley

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AMERICAN
PSYCHOLOGICAL
SOCIETY

1010 Vermont Avenue, NW
Suite 1100
Washington, DC 20005-4907
202-783-2077 Phone
202-783-2083 Fax

August 14, 1992

The Honorable George Bush
President of the United States
The White House
1600 Pennsylvania Avenue, N.W.
Washington, D.C. 20500

Dear President Bush:

I am writing to you on behalf of the American Psychological Society, which represents over 14,000 scientific psychologists engaged in behavioral research, to urge you to sign into law S.544, the "Animal Enterprise Act of 1992."

This legislation passed with overwhelming support in both houses of Congress and has been thoughtfully crafted by a diverse alliance of organizations including federal agencies, the biomedical and agriculture communities, animal welfare groups and the American Civil Liberties Union.

It is critical that our nation continue to attract and retain the best scientists possible to ensure that the life-saving and life-enhancing benefits of biomedical research will not be thwarted by the terrorist tactics of animal rights extremists. Only by protecting our researchers through federal legislation that will make it easier to prosecute these interstate crimes, will we continue the important progress that has been made toward alleviating human suffering.

We would greatly appreciate your timely support of this important legislation.

Sincerely,

Alan G. Kraut, Ph.D.
Executive Director

cc: Vice President Dan Quayle
The Honorable D. Allan Bromley

2497.

Rockywold-Deephaven Camps, Inc.

August 16, 1992

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

Dear Allan:

Your letter of July 14, addressed to me at the New York Times, came while I was in hiding trying to finish a book which was due on July 31. I finally handed it in on Friday, collected my mail and headed north to this refuge.

I would very much like to have interviewed Dr. Reilly, since I attended the original Stockholm Conference on the world environment. However, being retired, I did not go to the Rio one.

I made copies of your letter for Nicholas Wade, who is our Science Editor, and for Bill Stevens, who handles environmental stories and went to Rio. Nicholas said Bill Stevens would phone you.

It was a pleasure to recommend Joe Allen for the honorary degree. I know they choose the recipient very carefully, having been on the HOnorary Degrees Committee in the Giamatti era. I was especially happy to learn from you that Joe has been doing so well as a "business man."

Thanks for the invitation to the White House mess. The only time I have eaten there was many years ago with my former roommate, McGeorge Bundy.

With best wishes,

Walter S.

Walter Sullivan

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FROM: BARROW, ROBERT E.:NATIONAL GRANGE

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 08/14/92

SUBJECT: LETTER TO PRESIDENT BUSH REQUESTING THAT HE SIGN S.544, "THE ANIMAL ENTERPRISE PROTECTION ACT OF 1992".

****

DIRECTORATE ASSIGNED: STAFF ASSIGNED:

ACTION REQUIRED: STAFF ACTION:

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SENDER'S DUE DATE:

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COPIES TO: D. Allan Bromley
LIFE SCIENCES

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national grange

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Master, Robert E. Barrow

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August 14, 1992

The Honorable George Bush
The White House
Washington, D.C. 20500

Dear Mr. President:

On behalf of the approximately 300,000 members of the National Grange, I respectfully request that you sign S. 544, "the Animal Enterprise Protection Act of 1992".

This bill provides farms, ranches, research facilities, and legitimate animal exhibitions with the enhanced, federal protection they need from the growing radical activists' violence. The bill, passed by the House on suspension (with 264 co-sponsors) and by unanimous consent in the Senate, is a focused, balanced approach to those protections that were achieved by animal users, Congressional members, federal law enforcement experts, and animal welfare and legal groups.

This vital legislation enables state and local government authorities to draw upon and coordinate with federal experts and facilities when they are confronted by radical activists' criminal activity. In the last decade, there have been well over 100 recorded incidents in over 25 states, causing tens of millions of dollars in damage to vital food production and medical research. S. 544 will be a powerful deterrent to these actions.

The National Grange is an active member of a national coalition that consists of farmers, ranchers, agribusinessmen, biomedical and agricultural research facilities, colleges, universities, zoos, aquaria, rodeos, circuses, exhibition groups, and citizens organizations who have strongly supported S. 544 and the House companion bill, H.R. 2407. We have worked with the Agriculture and Judiciary Committees of both houses of Congress in reaching a compromise that deserves the nation's support.

We urge you to sign S. 544. On behalf of the Coalition members, thank you for your support of American agriculture and the continued use of animals in agricultural and biomedical research.

Respectfully,

Robert E. Barrow

Robert E. Barrow, Master
National Grange

REB/rfh
cc: The Honorable Dan Quayle
The Honorable Clayton Yeutter
Mr. D. Allan Bromley

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TYPE: INFORMATION DOCUMENT NUMBER: 9202707
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS

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FROM: TRULL, FRANKIE L.: NATIONAL ASSOCIATION FOR BIOMEDICAL RESEARCH

TO: PRESIDENT BUSH

DATE OF
CORRESPONDENCE: 08/13/92

SUBJECT: A REQUEST TO SIGN S.544, "THE ANIMAL ENTERPRISE ACT OF 1991".

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE:

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DATE COMPLETED:

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COPIES TO: LIFE SCIENCES
D. Allan Bromley

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CENTRAL FILES:

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NABR NATIONAL ASSOCIATION FOR BIOMEDICAL RESEARCH

August 13, 1992

The Honorable George Bush
President of the United States
Executive Office of the President
The White House
1600 Pennsylvania Avenue, N.W.
Washington, D.C. 20500

Dear President Bush:

On behalf of its 350 research-related member institutions, the National Association for Biomedical Research (NABR) respectfully requests you to sign S. 544, the "Animal Enterprise Act of 1992." S. 544 protects the public from the loss of lifesaving research and deters life-threatening crimes against animal facilities.

S. 544 is the result of three years of extensive and careful compromise involving the interests of Members of Congress, animal protection organizations, the American Civil Liberties Union and federal agencies, as well as the biomedical and agriculture communities. The legislation was passed on suspension by the House and by unanimous consent in the Senate. Given its wide support, including 264 cosponsors in the House and 32 cosponsors in the Senate, we believe S. 544 deserves your endorsement.

Unfortunately, animal rights extremists have continued with terrorist-type activities while Congress deliberated the need for federal protection of animal research facilities. Over the past ten years, there have been approximately 100 reported illegal incidents carried out by animal rights zealots, causing millions of dollars in damage and loss of irreplaceable research data. These crimes are committed on an interstate basis and must be addressed at the federal level. State and local authorities have been unsuccessful in apprehending and, therefore, prosecuting those responsible.

We urge you to sign S. 544 to protect this nation's researchers. Thank you for consideration of our views and your Administration's support of biomedical research.

Sincerely,

Frankie L. Trull

Frankie L. Trull
President

bc: The Honorable D. Allan Bromley

818 Connecticut Avenue, N.W. • Suite 303 • Washington, D.C. 20006 • (202) 857-0540 • FAX (202) 659-1902

(1)

Aug 8, 1992

Hi!

I was thinking about what I'd seen of bees since I saw no bees early in the summer, but in the past 3 weeks or so bees are around my potted flowers & vegetables I tried other kinds of pollination - by ants & other insects by just laying the pots down sideways on the ground - for ants or whatever. Some pepper plants are growing but others don't have any peppers yet. Wasps pollinate too, other red & black. But bees are needed for cross pollination. If the plants don't cross pollinate each plant may lose strength. I saw a huge patch of wild hepatica flowers & in a few spots where it was lower the pink & white flowers were purple about 2 years ago in N. Chagrin. My guess is a few grains of pollen washed into low spots. What it means I can't say. I mention it to the naturalist.

(2)

I'm wondering about colour since light is pale yellow, and is medium + sulphur is gold, and gold metal is one of the few metals which is richer colour than silver. (I think).

Yahweh was giving gold as small amounts to the people. Perhaps the use of gold was for plants + then went acting to people like use was Thapsibia. Mustard seed? Perhaps it was gold that came in in Bronze Age Canada when the atmosphere was so thick - 36. or 37. ??? ! ! There sparrows come back with a good colour. Sparrows, - birds who are a carrier of something perhaps thru their droppings. I'm wondering still, about a robin red breast + its nest droppings running down the tree trunk. (I wrote.) Maple tree, I think.

The reason I say all this has to do with bats stopping up hibernate when it's cold + chilly + not the sun coming in the sun. I'm thought

perhaps

Also I watch a bee bringing on a mangred plant, yellow & orange + brown. The mangels smell terrible to me but as I watched the bee, it opened its wings + looked my mind like a fly + they both have compound eyes. I thought it was a yellow jacket. It was striped brown + black a type of yellow. I in had flies at me lately, which is normal for infestation especially on boats. Fly also landed on my shirt when I was doing the nite + was arrogant in the morning.

I spoke on the average for a Bureau and suggested mulches might grow + pond mud, pulpy things squash, pumpkin, + animal potatoes + roots in the area where they might not have ants. Flowers especially yellow ones bees hibernate + mayn die if the cold is not due to plummet but something else.

In fact, maybe everyone was having a drinker problem

[illegible] for purple

[illegible] grass fertilizer [illegible] also [illegible] of wind + water [illegible] 1 [illegible] also be too much sometimes in water

with grapes, which are maybe fertilized another way. Wasps or worms. I looked at bunch of wild grape vines + saw something appeal but I can't remember, but in the woods in N. Chapin Park, opposite Gate N/ the apartment. I could be wrong.

I wrote about plants which sent to Lou were I grew checked. That is sweet water. Pinks, purple + white flowers. It might be the enzyme to the right side in the atomic chart. Purple white ~~pink~~.

Sincerely,
Jane Dixie Cary Howard

Though the Indiana men are not so sweet, but I still think the Fe(My) is of the lowest numbers which should actually build up on the earth. Perhaps the My. is between the electrons + proton nucleus + is rarer than usual. I understood that more purple or pink ones if the hydrogen were changing

seize to begin a new ruin ? ? ? Upon ruin
in a ruin's atmosphere itself. ? ? It's
logical & I have no idea what to
do about it but that's nuetrons.
Oregon's also has rent - at least
some a few months back. Was there
a freeze ? in California ? last winter ? That's
all I can add. The Indians
mens must have the same cold weather
for seven we have had here in Cleveland.

June Bug Around

And Gypsy moths have infested
the maple tree in this area. But
a maple tree by the street attacked maple
trees starting in Michigan about
15 years ago & spread East to Ohio.
and 8 years ago a man my pin oak
tree living the street had nearly
dying white larva on the tree trunks.
Some died.

Moths were coming out of
my 10th year. to cupboard which
was (again & again) behind the Third T. V. outside against the wall
which I thought was the reason it
was warm enough to lay eggs. I did
wonder if the dust on the
moths wings (white) ? June

(6)

If the scent of Scotch whisky is aging in oaken barrels, would that mean the worm returning to the wood - ? gum and contaminate a human body in little bits of the worm? Maple syrup is boiled.

Jenne

Jeanne Irene Cary Howard
1589 Harvchurst Rd
Cleveland, O. 44124

CLEVELAND OH
PM
10 AUG
1992

President Geo. H. Bush
Senior Advising Committee
White House
Pennsylvania Ave.
Washington, D. C.

to: Assistant to the president
Science + technology
D. Allan Bromley
Washington, D.C.

July 20th 92

Dear assistant to the president Bromley;

I understand there is a cash reward, benefits, awards, a nabel prize + a check $700,000 to the person that discovers the cause of cancer.

I also understand there is a larger cash reward, benefits, awards, a nabel prize + a check $700,000 to / for the person that discovers the cure of cancer.

If you are interested in knowing the cause of + the cure of / for cancer, You will contact me. I have known the cause + the cure of / for cancer. Be prepared to see to it that I get all that goes to the person that discovers the cause of + the cure of / for cancer. all cash rewards, benefits, awards, two nabel prizes + the two checks that go with the two nabel prizes about $1,406,000. Everything.

I can assure you tobacco + tobacco products do not cause cancer. Cigarettes, cigars, pipe, chewing tobacco ~~snuff~~, etc., do not cause cancer.

alcohol of any kind / type does not cause cancer.

I can add one other of earths natural elements to the table / chart of all the earths natural elements.

I can explain the cause of arthritis, nausea, gaut, ringing in the ear(s) migrain headaches, mental depression, confusion, nervesness, leg + stomach cramps other body aches + pains + physical discomforts. I can explain the cause of the Flu. The Flu is not caused by a Flu "Bug."

I can tell you who the mafia is, + all there disguised names are + where there headquarters are for all organized crime in the United States.

I can tell you how the love name Housing system is destroyed + respectfully Richard D. Spurling.

20 N. Roessler St. apt # 620
Monroe, Mich. 48162

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TYPE: ACTION
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DOCUMENT NUMBER: 9202241
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DIRECTORATE STATUS

****

FROM: WEISBURGER, John H.: WEISBURGER ASSOCIATES

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 07/29/92

SUBJECT: HE IS WRITING REGARDING THE AVAILABILITY OF NIH GRANTS.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED:

ACTION REQUIRED: AS APPROPRIATE

STAFF ACTION:

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SENDER'S DUE DATE:

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WEISBURGER ASSOCIATES
4 WHITEWOOD ROAD
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USA

JOHN H. WEISBURGER, PhD, MD (hon)

(914) 592-4037

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July 29, 1992

Dr. D. Allan Bromley
Director, Sc + Techn. Policy
Washington DC 20506

Dear Dr. Bromley

The U.S. Congress, and voluntary groups like the American Heart Association and the American Cancer Society, have generously supported medical research over the last 30 years. Much progress has been made. There is a better understanding of the mechanisms underlying the causes of major chronic diseases, heart disease, stroke and many types of cancer. This is the basis for sound preventive actions, with ensuing successes, like the decline of deaths from heart disease, stroke, and even lung cancer in men. When AIDS arose as a new problem, it could be attacked promptly, because of extensive experience with viruses in cancer research.

Thus, medical research has been a cost-effective investment, saving expensive hospitalization and medical care costs, and extending disease-free life span.

Yet, considering the magnitude of the US health problems, funds for research have not kept up in the last 10 years. NIH grants are much harder to get. Young physicians and scientists do not join the battle.

Considering the base of fundamental knowledge, rapid progress in prevention, the optimal and cheapest means of disease control, could be made yet in this century, if more funds were available.

Funds in research are investments. The pay-back in lower medical costs and more cost-effective technology is rapid. The NIH and NSF budgets should be doubled **now**, and tripled in an orderly fashion over the next 7 years.

Dr. Coller and I have published the attached articles, in which we call for a re-direction of unneeded defense to civilian research, especially medical research. We are employers too, in every State and Congressional district!

Sincerely yours,

John H. Weisburger

JOHN H. WEISBURGER, Ph.D., M.D.(hc)

VOLUME VIII NUMBER 4
SUMMER 1992

ISSUES
IN SCIENCE AND TECHNOLOGY

National Academy of Sciences
National Academy of Engineering
Institute of Medicine

Recent articles in the Spring 1992 *Issues* by Sidney D. Drell and Jacques S. Gansler ("Restructuring the Defense Industrial Base") deal with rearranging the U.S. national defense effort in view of the dramatically altered international situation. Yet the Senate recently voted a budget of $292 billion for defense, and it seems likely that defense budgets with only minor reductions from those prevailing in the Cold War years will end up on the president's desk in the future.

It appears that Congress and the executive departments fear that a rapid reduction in defense dollars would put skilled technicians, engineers, and scientists out of work. This concept, however, is erroneous. We in civilian scientific and biomedical research are starved for research dollars. If funds were available, we could recruit people not needed in the defense industries, employing scientists, engineers, physicians, and biomedical researchers. We also employ grant and contract managers and could use staff from defense who are experienced in program administration.

The budgets of the National Institutes of Health (NIH) and National Science Foundation (NSF) are not growing commensurately with the national need for research in areas yielding direct tangible benefits, such as biomedicine. In the case of NIH, with which I am most familiar, only 18 to 25 percent of meritorious peer-reviewed grants are actually funded.

Therefore, a wise move by Congress and the president would be to immediately reduce defense expenditures by 50 percent and make those funds available to the NIH, the NSF, and to small manufacturers (whose support Philip Shapira advocates in "Lessons from Japan: Helping Small Manufacturers," also in the Spring issue). This would very quickly provide an increase in sound research and education. At present, grants have been approved but not funded. Scientists and physicians are ready to hire people, buy equipment, and upgrade facilities and libraries. Defense money in such hands will be wisely used for the benefit of the world's people.

In hindsight, we can say that Japanese and German progress in science and technology over the past 30 years was facilitated because many of their key national resources were not consumed by defense and could be used to develop major civilian science- and technology-based enterprises. We now have the opportunity to really earn a peace dividend by a prompt realignment of our national priorities toward advanced scientific, technological, and medical research. All benefits, no risks. Let's proceed now.

JOHN H. WEISBURGER
Senior Member and Director Emeritus
American Health Foundation
Valhalla, New York

Economic Benefits of Biomedical Research Support

AFTER 4 YEARS OF EFFORTS TO INCREASE support for the National Institutes of Health (NIH) budget as a member of the American Society of Hematology Committee on Public Information and Governmental Affairs, I have come to appreciate the importance of complementing our usual appeal based on humanitarian concerns with more focused economic arguments. Recently, I wrote to members of Congress with an initiative to increase the number of grants supported by the NIH as an *anti-recession program.* Among the arguments I made were:

1. The money will not be wasted on a program of untested benefit, but rather will be spent on research that has already been judged highly meritorious. All projects that will be funded under this proposal will have been through the elaborate NIH peer review mechanism and judged either "excellent" or "outstanding" by a panel of leading scientists.

2. The money can flow immediately and will be spent rapidly, avoiding the problems economists have noted in developing new programs for funding or funding large projects that require prolonged lag times to establish specifications or let competitive bids. Nearly all investigators who have submitted unfunded research proposals would be able to initiate their projects and begin spending the money within days.

3. The money spent on NIH grants has a high multiplier effect on the U.S. economy. The largest component of NIH grant funds goes to personnel costs for scientists, technicians, nurses, laboratory aides, data coordinators, and secretaries who represent a broad cross section of the American middle class. The NIH Director's Office estimates that the 1990 RO1 and PO1 grants led to the full-time equivalent employment of more than 53,000 individuals. The supplies and equipment purchased with NIH grant funds are overwhelmingly spent on equipment and reagents made in the U.S. The corporations supplying equipment and reagents range from very large conglomerates to very small boutique companies that are just emerging. An expansion of NIH funding will help to secure the future of these high-technology smaller companies, many of which are likely to develop major export programs because of the uniqueness of their products and the increase in biomedical research in Japan and Europe. Finally, the increasing collaborative nature of science and the need for scientists to gather at meetings require that scientists travel frequently, giving a boost to the domestic airline and hotel industries.

4. Funds spent on NIH grants will diffuse geographically throughout the U.S. economy with particular emphasis in urban centers that have been particularly hard hit by the recession. The financial benefits will not be restricted to these areas, however, because the companies that supply biotechnology equipment and reagents are broadly distributed throughout the U.S.

5. The funds will help the "infrastructure" of the United States economy by increasing the "intellectual capital" that lies at the base of the biotechnology industry, one of the emerging U.S. industries with strong export potential. Data from NIH indicate that in 1990 $1.23 billion of NIH funds went directly to biotechnology research and another $1.74 billion went to projects indirectly related to biotechnology. The Industrial Biotechnology Association recently reported that there are now approximately 1,100 biotechnology-related companies employing 50,000–60,000 individuals. As an example of the importance of this relationship in hematology, NIH funding of Dr. Eugene Goldwasser's laboratory at the University of Chicago led to important discoveries concerning erythropoietin that contributed significantly to the early success of Amgen, a major biotechnology company with many hundreds of employees and hundreds of millions of dollars in sales each year. Moreover, NIH funds not only lead directly to new discoveries, but also train new generations of scientists, further increasing the intellectual infrastructure of the U.S. In 1990, there were more than 12,000 trainees and fellows supported by NIH.

6. NIH research is the source of medical advances that make American medicine the most sophisticated in the world. Although there is a tendency to focus on the high-technology techniques and expensive therapeutics that have resulted from such research, NIH funds have also been crucial in deciphering basic mechanisms of disease and identifying risk factors that are the basis of inexpensive, preventive medicine strategies. Thus, much of the work on blood cholesterol and hypertension as risk factors of cardiovascular disease has been funded by NIH.

7. U.S. economic productivity depends on the health of U.S. workers and their families. Consider the effect of improved treatment for heart attacks on the ability of American workers to reach their economic potential.

8. Basic research is a crucial component of medical cost containment, the most serious challenge facing the U.S. economy. One remarkable example is found in the history of aspirin as an antithrombotic agent. Some of the most important initial basic research on the antiplatelet effects of aspirin was performed independently in the laboratories of Drs. Harvey Weiss and Marjorie Zucker in 1967–1968, both of whom were funded by NIH. Aspirin was subsequently shown to significantly decrease the risk of death from heart attacks, and to prevent recurrent heart attacks and strokes. It is not inconceivable that the total direct and indirect cost savings from the discovery of aspirin's antiplatelet effects exceeds the entire NIH budget this year. In a recent analysis of cost savings resulting from other selected NIH research support, an investment of $800 million was found to produce a 1-year savings of between $5.2 billion and $6.7 billion (1).

9. NIH supports industrial research directly through the Small Business Innovation Research program; more than 650 grants totaling $74 million were funded in 1990.

10. Support of medical research is consistently a top priority of the citizens of the U.S. Harnessing the power of the scientific method for the alleviation of human suffering from disease is the proudest achievement of the human race. Spearheading that effort for the entire world for the past 45 years has been the NIH, supported by the American people and their Congressional representatives.

Economic considerations are likely to be extremely important in determining the distribution of the very limited amount of discretionary funds available to the Federal Government for the foreseeable future. It is important, therefore, for the biomedical community to collect and analyze data concerning the economic benefits of NIH funding. These data will broaden our support at all levels of government and improve our chances of obtaining additional funding.

Barry S. Coller, M.D.
Professor of Medicine and Pathology
Head, Division of Hematology
State University of New York at Stony Brook
Stony Brook, New York 11794, USA

REFERENCES

1. *Cost Savings Resulting from NIH Research Support.* NIH Publication NO. 90-3109, October, 1990

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FROM: MALONEY, STACY: SOUTHWEST FOUNDATION FOR BIOMEDICAL RESEARCH

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 07/10/92

SUBJECT: SUMMARY ANNOUNCING LT. GEN. FRANK LEDFORD HAS BEEN NAMED PRESIDENT OF THE SOUTHWEST FOUNDATION FOR BIOMEDICAL RESEARCH.

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

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SENDER'S DUE DATE:

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Southwest Foundation
for Biomedical Research

7620 N.W. Loop 410
P.O. Box 28147
San Antonio, Texas 78228-0147
(512) 674-1410

92 JUL 27

Media contact: Stacy Maloney
512/ 674-1410

SUMMARY: Ledford takes SFBR command

July 10, 1992

FOR RELEASE UPON RECEIPT

SAN ANTONIO -- Lt. Gen. Frank F. Ledford Jr., the Army Surgeon General who mobilized the largest medical force since World War II in Operation Desert Storm, has been named president of the Southwest Foundation for Biomedical Research, SFBR board chairman George C. Hixon announced today.

Ledford, 58, a nationally renowned leader in military medicine, has been Surgeon General of the Army since 1988, serving as CEO of the largest comprehensive health care system in the U.S. Based in Falls Church, Va., the Army Medical Department operates 50 hospitals, 197 clinics, 14 biomedical research laboratories, medical supply facilities and academies, and employs 96,000 military and civilian personnel.

Under federal law, the Surgeon General's term of office is four years, and Ledford completed his term June 30, retiring as a three star general after he was confirmed by the U.S. Senate. Highlighting 34 years of Army service as a doctor, Dr. Ledford received the Distinguished Service Medal -- the nation's highest peacetime award -- presented recently by Army Chief of Staff Gen. Gordon Sullivan, and the U.S. Surgeon General's Medal, the Public Health Service's top award.

"We are extremely pleased that Dr. Ledford will take over the leadership of Southwest Foundation at this key time in our history," Hixon said. "His intellect, medical expertise and vigor will be vital in maintaining and accelerating the Foundation's stature as a world-class biomedical research center, including the Foundation's eventual move to the Texas Research Park."

(more)

Ledford's selection follows a nationwide search for a successor to Dr. Duncan Wimpress, who retired May 1 after a 10-year SFBR presidency. Founded by oilman Tom Slick in 1941, SFBR is a non-profit organization dedicated to improving human health through leading-edge biomedical research. Ledford will assume his new duties Monday, Aug. 3.

An orthopedic surgeon, Ledford calls San Antonio his "emotional home," noting that he was responsible for a second Army Medical Department headquarters at Fort Sam Houston, the Health Services Command, which directs the activities of 38 domestic hospitals. Ledford also was an intern there at Brooke Army Medical Center from 1959-60. He and his wife Marilyn have one daughter, Cheryl, who will be a first-year medical student this fall at the University of Texas Health Science Center at San Antonio.

"The Desert Storm mobilization is among my greatest accomplishments," Ledford said. "The Medical Corps included 25,000 Reservists and 44 Army hospitals were deployed to the Persian Gulf while evacuation facilities were upgraded in Europe and the U.S."

In addition, Ledford's accomplishments as Surgeon General of the Army include holding costs on medical inflation to 7 percent compared to 11 percent nationally, gaining major legislation for higher physician and nurse compensation, planning for two new medical centers, revising the medical wartime doctrine, redesigning peacetime health care for 3.4 million beneficiaries, an enrollment-type of health care partnership with the civilian health care industry.

A native of Jacksonville, Fla., Ledford received his M.D. degree from the University of Cincinnati College of Medicine in 1959 and served his residency in surgery at Womack Army Hospital at Fort Bragg, N.C., from 1960-61; in orthopedic surgery at Letterman Army Medical Center in San Francisco from 1961-64; and

in children's surgery at Phoenix Crippled Children's Hospital from 1964-65. He received a B.S. degree from the University of Dayton in 1955 and was in ROTC.

Among his high-level administrative accomplishments, Ledford served as commanding general of the 7th Medical Command in Europe from 1985-88 and Letterman Army Medical Center in San Francisco from 1982-85; he was an "ombudsman" as chief of the Medical Corps Affairs, Office of the Surgeon General, in Washington, D.C. from 1980-82, and commanded the U.S. Army Medical Activity, Fort Riley, Kansas, in 1980. He also was chief of graduate medical education in the Surgeon General's Washington office during 1973-76 where he earlier was assistant surgical consultant. He held various surgical appointments during 1965-72, including a one-year stint as chief of surgery at a 400-bed evacuation hospital in Vietnam, performing hundreds of operations and supervising 16 surgeons.

Ledford is a member of numerous professional societies and is certified by the American Board of Orthopedic Surgery. His military decorations include the Distinguished Service Medal, Cross of Honor in Gold by the Federal Republic of Germany, Legion of Merit, Meritorious Service Medal, Army Commendation Medal with Oak Leaf Cluster; Vietnam Service Medal and National Defense Service Medal.

# # #

"Document Control for Division of Life Sciences"

TYPE: ACTION
DOCUMENT NUMBER: 9202511
ORIGINATOR: 02
STATUS I
DIRECTORATE STATUS C

****

FROM: BLAIR McCORMICK, William Mrs.

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 07/04/92

SUBJECT: SHE IS WRITING WITH RECOMMENDATIONS REGARDING THE INVESTIGATION OF AN AIDS VACCINE, AND SHE ASKS IF DR. BROMLEY COULD FORWARD THE ENCLOSED EDITORIAL ON FETAL TISSUE RESEARCH TO THE PRESIDENT.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED: D.A. Henderson

ACTION REQUIRED: FOR DAB'S SIGNATURE

STAFF ACTION: AS APPROPRIATE

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SENDER'S DUE DATE:

OSTP DUE DATE: 08/04/92

STAFF DUE DATE 08/04/92

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COPIES TO: D. Allan Bromley

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

July 22, 1992

Dear Deeda,

I fully share your interest in and concern for our efforts to proceed expeditiously with HIV vaccine field testing. The problem is a complex one but I am happy to report that the special working group is making good progress. Don Burke himself plays an especially important role as Vice-Chairman of the working group and members of the committee maintain very close contact with Max Essex and his highly productive and imaginative group. Development of an effective vaccine is an important challenge demanding of the very best efforts we can muster!

Sincerely yours,

D. Allan Bromley
Director

Mrs. William McCormack Blair
2510 Foxhall Road
Washington, D.C. 20007

Sorry I was already very late for an appointment when our paths crossed recently at NIH!
DAB

2511

2510 FOXHALL ROAD
WASHINGTON, D. C. 20007

RECEIVED
92 JUL 21 A10:
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MAIL ROOM

July 4, 1992

Dr. D. Allan Bromley
Assistant to the President
for Science and Technology
Old Executive Office Building
17th and Pennsylvania Avenue
Washington, DC 20500

Dear Allan,

Thank you for your letter. I was happy to learn that you have created a special working group to develop a coordinated plan for vaccine testing. The other evening when Dr. Essex was here I had a group of scientists for dinner with him which included Don Burke from Walter Reed. If you or Dr. Henderson have by any chance not encountered Dr. Burke, he seemed absolutely terrific and he is very much focused on the organization of future AIDS vaccine trials in northern Thailand. If this working group is still holding meetings, they might find it interesting to schedule talks from Dr. Essex at the Harvard School of Public Health or Dr. Tun Hou Lee. As you are aware they discovered GP 120/160 which, it is my understanding, is the antigen being used in ten out of twelve of the candidate vaccines now in phase I trials and they have already through selective site specific deglycosolation developed ways for better antigen presentation.

Is there any way in the world, even in the stealth of night you could find a way to slip this excellent editorial from Science on the desk of the President? It would be sad to think that his mind was closed to a reasonable discussion of the issue. I know the President has said he would "do what he had to do " to win re-election, but does he have to impede the progress of science?

All the best,

Deeda

Mrs. William McCormick Blair, Jr.

Is there any way in the world, even in the stealth of night you could find a way to slip this excellent editorial from Science on the desk of the President? It would be sad to think that his mind was closed to a reasonable discussion of the issue. I know the President has said he would "do what he had to do " to win re-election, but does he have to impede the progress of science?

All the best,

Deeda

Mrs. William McCormick Blair, Jr.

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EDITORIAL

Fetal Tissue Research

For the second year in a row the National Institutes of Health budget authorization has been subject to a rider that approves fetal tissue research, but as a result the entire bill is threatened with a presidential veto. This mixture of politics and research is illogical and likely to damage both research and good political practice.

Fetal tissue research should have as little relation to the abortion issue as organ transplants have to automobile accidents or suicides. Tissues and organs from automobile accident victims played a major role in the development of sound organ transplant therapies, but no one argued that such research justified or legitimized automobile accidents. In the same way, the decision to use fetal tissue for research is made separately from the decision of an individual to have or not to have an abortion. No scientist should be involved in soliciting an abortion in order to obtain material for research, but to limit materials for research on the grounds that one is taking a stand on the abortion issue is an illogical and counterproductive path that can only damage all participants. Research on fetal tissue should be placed in the same category as research on cadavers, on the use of tissues from victims of accidents, and so forth. It is a situation in which the fundamental decisions have already been made, and the scientist is then in the position of making the best of the consequences of a previous history. The commission appointed by President Reagan considered the issue carefully, did not condone abortion, but made clear that the issue of abortion should be separated from these issues of fetal tissue research.

Fetal tissue is of enormous value and can be used in actual therapy for certain illnesses like Parkinson's disease. Because fetal tissue is still undergoing growth differentiation, it is particularly valuable for understanding these processes and can be more easily adapted to diverse experimental circumstances than is adult tissue. Human fetal tissue has been introduced into mice to study the interactions of the AIDS virus with the human immune system, a situation that would be impossible to study in human volunteers because of the fatal characteristics of the AIDS virus and because there is no good animal model. Fetal tissue was also important in developing the polio vaccine. In the long run, fetal tissue will never be such an abundant source as to be used routinely for therapy, but it could lead to the development of cell lines or drugs that could be the basis of large-scale therapy.

Another advantage to studying fetal development and fetal tissue is that new procedures are developed that work best or only during gestation to treat disease conditions in fetuses. There are also new techniques for direct intervention during the pregnancy period, such as procedures that will assist in organ transplants at a later time. The injection of cells of a diseased organ, for example, the liver, before the twelfth to thirteenth week of pregnancy has the potential to induce a state of tolerance that diminishes or prevents rejection of the transplantation of that organ later in life. Thus, fetal research may be of particular benefit to those women who are agonizing over the heartrending decision between abortion and bringing a child with predictable lifelong difficulties into the world. The compromise requiring that only tissue from natural abortions be used in research and treatment is not a real option, because such tissue is usually received in poor condition and is frequently inherently unusable for the reason that the natural miscarriage is caused by fetal malfunctions that might be viewed as nature's way of eliminating a potentially defective child.

The sooner this particular game of politics is ended the better. Research on fetal tissue has great promise of benefit to all. It neither justifies nor negates the highly personal individual decision to have an abortion, and therefore the use of those materials should be termed as unrelated to the political issues. Research on cadavers is neither pro- nor antideath. It treats death only as a fact after which as much constructive future knowledge as possible could be built. In the case of fetal tissue research, a death is preordained outside the research world, but proper timing and intervention can develop knowledge and therapy for future benefits. It is time to proceed with those constructive approaches with professionalism and without emotionalism.

Daniel E. Koshland, Jr.

"Document Control"

TYPE: INFORMATION DOCUMENT NUMBER: 9202113
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS
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FROM: FARLOW, JAMES: INDIANA UNIVERSITY PURDUE UNIVERSITY

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 07/03/92

SUBJECT: LETTER TO THE PRESIDENT CONCERNING THE REQUEST OF MR. PETER LARSON, PRESIDENT OF THE BLACK HILLS INSTITUTE OF GEOLOGICAL RESEARCH, THAT THE SPECIMEN OF "TYRANNOSAURUS REX" BE RETURNED TO BHI.

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

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SENDER'S DUE DATE:

OSTP DUE DATE:

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PURDUE UNIVERSITY
AT FORT WAYNE

Department of Geosciences
(219) 481-6249

213

RECE
92 JUL 27 AM : 3
OSTP
MAIL ROOM

July 3, 1992

President George Bush
White House
Washington, D.C. 20510

Dear President Bush:

I am writing in support of the request of Mr. Peter L. Larson, President of the Black Hills Institute of Geological Research, that the splendid specimen of Tyrannosaurus rex collected by the Black Hills Institute (BHI 2033, alias "Sue"), be returned to BHI until legal matters concerning the ultimate repository of this specimen are settled.

Although I candidly admit that I have mixed feelings about the role of commercial collectors in the field of vertebrate paleontology, I nonetheless believe that Mr. Larson and the BHI have behaved in a responsible manner in their collection and preparation of Sue. Working with a number of professional paleontologists, myself included, Mr. Larson has begun organizing an interdisciplinary panel of experts to consider various aspects of the systematics and paleobiology of Tyrannosaurus rex. Plans for the meeting of this group have now been put on hold, due to the inaccessibility of one of the best, most complete specimens of the dinosaur--that is, Sue. Mr. Larson is even more concerned over the possibility that the specimen might be damaged due to improper storage or packing during shipping. Although I am not qualified to comment on which institution should ultimately house BHI 2033, I do think it appropriate for Sue to be returned to the Black Hills Institute for proper conservation and preparation, and to allow scientific study of this incalculably significant specimen to proceed, until such matters are resolved.

Thank you for your consideration.

Sincerely,

James O. Farlow

James O. Farlow
Professor of Geology

cc: The Honorable William Barr, U.S. Attorney General
The Honorable Manuel Lujan, Jr., Secretary of the Interior
Mr. Irvin Mortenson, Badlands National Park
The Honorable Larry Pressler, U.S. Senator
The Honorable Richard Cheney, Secretary of Defense
The Honorable George Mickelson, Governor of South Dakota
Mr. Kevin Schieffer, U.S. Attorney
Dr. D. Allan Bromley, Assistant to the President for Science and Technology
The Honorable Tom Daschle, U.S. Senator
The Honorable Tim Johnson, South Dakota Congressman
Mr. Harlen Watson, Department of the Interior

Fort Wayne, Indiana 46805-1499

Mr. Malcome Browne, The New York Times
Mr. Roger O'Neil, NBC News
Mr. Peter Larson, Black Hills Institute

"Document Control"

TYPE: ACTION DOCUMENT NUMBER: 9202526
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS

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FROM: TATE, Robert

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 06/28/92

SUBJECT: HE IS WRITING TO URGE THAT THE SKELETAL REMAINS OF THE TYRANNOSAURUS REX THAT WERE SEIZED FROM THE BLACK HILLS INSTITUTE IN SOUTH DAKOTA BE RETURNED.

****

DIRECTORATE ASSIGNED: PHYSICAL SCIENCES

STAFF ASSIGNED: Dave C.

ACTION REQUIRED: AS NECESSARY

STAFF ACTION:

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SENDER'S DUE DATE:

OSTP DUE DATE: 08/04/92

STAFF DUE DATE

DATE COMPLETED:

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

August 10, 1992

Dear Mr. Tate:

Thank you for your recent letter to Dr. Bromley regarding the recent seizure of the Tyrannosaurus rex skeleton from the Black Hills Institute of Geological Research. I am sure you realize that Dr. Bromley cannot get involved in a criminal investigation, but I thought you would like to know that we are inquiring as to the storage conditions and treatment that the skeleton receives while in the custody of the FBI. We will try to ensure that the scientific value of the remains are preserved while the courts decide the legal issues involved. Thank you for bringing this issue to Dr. Bromley's attention.

Sincerely yours,

David C. Cranmer
Fellow

Mr. Robert Tate
RR Box 328
Clearfield, SD 57580

2526

RR Box 328
Clearfield, SD 57580
June 28, 1992

RECEIVED
92 JUL 21 AM 10 39
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MAILROOM

D. Allan Bromley
Assistant to the President for Science & Technology
Executive Office Building
Washington, DC 20240

D. Allan Bromley:

I would like to introduce myself. I am a twenty-nine year old rancher, landowner, and amature paleontologist. Also, I was a member of the excavation crew which assisted the Black Hills Institute of Geological Research in their recovery and preservation of the fossil remains of the largest and most complete Tyrannosaurus rex known to this time.

I have been associated with the Larsen Brothers of the BHIGR since 1976, when as a thirteen year old boy I would ride my bike to the mailbox at the main road where they would pick me up and allow me to help at the dig for a mastadon. They took me under their wing and introduced me to the wonderful world of the past. They taught me identification methods and proper proceedures for recovery of fossils. Somehow, I don't think that very many people with their expertise would have taken the time for a kid interested in fossils. Now I like to think because of that, I can give some youngster some encouragement or explanation concerning the rock he or she may have found along the driveway.

I have watched the boys from Hill City go from what amounted to a rock shop along the highway to a world-renowned private paleontological research institution. The BHIGR has made many discoveries available to the scientific world at their own expense As a guest on collection expeditions I have been witness to their unselfish sharing of knowledge and technique with educators and students from all over the country. All without costing the American Taxpayers a cent.

On May 14th a man-made tradgedy occured. A great scientific resource was seized from the people who had discovered and labored over it. Arrangements for further scientific analysis and sharing had to be canceled. Now "SUE", the tyrannosaurus rex, lies rotting in government storage at taxpayers expense. With her lies the hopes and dreams of her free enterprise excavators, the promise of a museum to boost the economy of Hill City, and aspirations of several 'kids on a bicycle' such as I once was.

We must not let government bureaucracy squelch free enterprise in the field of science under the guise of the good of the people and ambiguous laws. We must return "SUE" to the Black Hills Institute of Geological Research.

Please convey my concerns to the President.

Sincerely,

Robert Tate

Charlee

"Document Control for Division of Life Sciences"

TYPE: ACTION DOCUMENT NUMBER: 9202239
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

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FROM: HUMPHREYS Robert E.: UNIVERSITY OF MASSACHUSETTS

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 06/11/92

SUBJECT: HE IS WRITING SUGGESTING THAT DR. BROMLEY AND THE ADMINISTRATION LOOK INTO THE NEEDS OF STATE SCHOOLS AND MEDIUM SIZED BIOTECH FIRMS.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED:

ACTION REQUIRED: AS NECESSARY

STAFF ACTION:

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SENDER'S DUE DATE:

OSTP DUE DATE: 07/06/92 STAFF DUE DATE

DATE COMPLETED: DATE COMPLETED/DEPT: 06/22/92

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COPIES TO: D. Allan Bromley

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REMARKS: NOTE: THIS IS A PERSONAL LETTER TO DR. BROMLEY AND, AS SUCH, CANNOT BE ANSWERED BY ANYONE IN DLS. PLEASE REASSIGN TO THE FRONT OFFICE.

OSTP RECEIVED: 06/22/92 DEPT RECEIVED: 06/22/92

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FROM: HUMPHREYS Robert E.: UNIVERSITY OF MASSACHUSETTS

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 06/11/92

SUBJECT: HE IS WRITING SUGGESTING THAT DR. BROMLEY AND THE ADMINISTRATION LOOK INTO THE NEEDS OF STATE SCHOOLS AND MEDIUM SIZED BIOTECH FIRMS.

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DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED:

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2239

University of Massachusetts
Department of Pharmacology
University of Massachusetts Medical Center
55 Lake Avenue North
Worcester, MA 01655
(508) 856-2151
FAX: (508) 856-5080

92 JUN 13 08
MAILROOM

June 11, 1992

Dr. D. Allan Bromley
Scientific Advisor to the President
The White House
Washington D.C.

Dear Dr. Bromley:

It was a pleasure to see the presentation of the honorary Doctor of Science degree to you at Fordham University recently. It has been many years since we worked together on the creation of The Gibbs Society. Each of us continues to push for the principles for which that group was founded.

Please permit me to inform you about developments at the University of Massachusetts Medical School testing the relationships between academic and corporate research groups and offering an experimental focus for the evolution of national policy to encourage and support such ventures. We present at this Medical School and the adjacent Biotechnology Park (in the 25 acre former Worcester State Hospital property) a good experiment to sort out policy issues, enhance synergies between corporate, and academic and governmental interests. At premium universities, large companies give multiyear, multimillion dollar grants to Departments and sections to create a wide range of new biotechnology products. In a smaller setting, but with still many excellent labs, we must be more agile to develop individual as contrasted to bloc relationships. It becomes difficult sometimes to discern the rules or guidelines for these efforts and we do not have vast legal resources to research and advise us on these matters. Governor Weld is firmly committed to helping (pushing) us into greater self-sufficiency in part through cooperative efforts with industry. We welcome that opportunity and are building bridges to companies around us.

Among the series of issues you and your colleagues need to address, please do look carefully at the needs of the excellent state schools and small to medium size biotech companies. Generally, we do not have the resources in legal departments, administrative depth and capital as do the great institutions and companies. But the quality is there and clarity of an encouraging and simply presented policy from the governmental level can catalyze more rapid development of such cooperative ventures.

Much has happened since our previous collaborations at Yale. My older son Dave was Lord of the Manor at the *Encaenia* at Fordham preceding the graduation ceremony. He was in China for 6 months

and next year will be in the Marine Corps in boot camp and an intelligence school. Eventually he plans on law school and some form of national service. Dan, my youngest son, is at Northeastern in criminal justice and will be in Dragon School at Camp Lejeune this summer. At Parris Island last summer he broke a 9-year record in nighttime orienteering and some Captain said he'd recommend him to 8th and I if he applied. Barbara and I are resettling into a quieter house.

My own research focuses on the mechanisms of antigen processing and has migrated to some issues in protein folding which are relevant to the scavenging of excised fragments of antigen proteins. I enclose a paper basically created by Stephen Vazquez and Dennis Kuo, two participants in an NCI minority student summer research program. I continue to prioritize the training of individuals both in the lab and at an institutional level.

Sincerely,

Robert E. Humphreys

Robert E. Humphreys, M.D., Ph.D.
Interim Chair of Pharmacology
Professor of Pharmacology and Medicine

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 267, No. 11, Issue of April 15, pp. 7406-7410, 1992
Printed in U.S.A.
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Residues in the Longitudinal, Hydrophobic Strip-of-helix Relate to Terminations and Crossings of α-Helices*

(Received for publication, November 1, 1991)

Stephen R. Vazquez‡§, Dennis Z. Kuo‡¶, Christopher M. Bositis‡‖, Larry W. Hardy‡**, Robert A. Lew‡, and Robert E. Humphreys‡ ‡‡§§

*From the Departments of ‡Pharmacology and ‡‡Medicine and the **Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01655*

An α-helix terminates when the virtual extension of its most hydrophobic, longitudinal strip containing Leu, Ile, Val, Phe, and Met lacks those residues. In each of 247 helices a template (□○○○□○○○□○○○□○○○○) was fitted to maximize the mean hydrophobicity of □ positions forming a longitudinal strip-of-helix. The template was then extended into sequences beyond the ends of the helices. Leu, Ile, Val, Phe, and Met occurred in □ positions in the longitudinal strip-of-helix at an increased frequency ($p < 0.001$), but in the first and second □ positions beyond either end of each true helix, they occurred at the same frequency as for their empirical distribution over all the proteins. Excesses of Asp and Glu were found in the N-terminal loop, and of Arg, His, and Lys in specific positions about the C terminus of helices. The longitudinal hydrophobic strip, the smallest amino acid in that strip, and charged amino acids in that strip, related to rotational and longitudinal orientation of α-helices in 15 proteins. Adjacent helices generally crossed through their longitudinal hydrophobic strips. They usually crossed through the smallest residue in the strip. Charged residues, when they occurred in the strips, were excluded from the crossing regions.

We have proposed that helix formation is determined principally by the formation and extent of a longitudinal, hydrophobic strip of Leu, Ile, Val, Phe, and Met along one side of an α-helix. To test this hypothesis, we examined the distributions of those amino acids within such hydrophobic strips in 247 helices and virtual extensions as helices of sequences around the true helices. The longitudinal hydrophobic strip in an α-helix was defined by fitting the primary amino acid sequence of the helix with a template □○○○□○○○□○○○□○□○○○□○○○○ to maximize the strip-of-helix hydrophobicity index (SOHHI,[1] the mean hydrophobicity of residues in □ position in the template (1, 2)). In helices of crystallized proteins such □ positions were usually aligned along the surface of the helix in a longitudinal strip (2). Such □ positions were assigned to quadrant III in the sheet projection (Fig. 1) and were filled principally with Leu, Ile, Val, Phe, and Met, with Asp, Glu, Lys, Arg, Asn, and Gln being excluded from that quadrant (2).

We have used the method of fitting the strip-of-helix hydrophobicity template to the primary sequence of helices to identify residues which would have fallen in the longitudinal hydrophobic strip of the virtual extension of helical structure into the adjoining sequences. In a nascent protein the longitudinal hydrophobic strip may stabilize coiling of successive loops of a helix against a coalescing hydrophobic region (1). In globular proteins, α-helices are frequently amphipathic (3–5). We tested the hypothesis that the lack of a hydrophobic residue in the first □ position beyond the helix determined termination of the helix. Other residues near the ends of helices may also stabilize or terminate helical structure, *e.g.* Asp, Glu near the N terminus, Arg, Lys near the C terminus, Asn, Pro at the N terminus (6–8). The location and chemical character of such stabilizing residues could be well defined in terms of the best-fitted strip-of-helix hydrophobicity template (1, 2).

We also tested the orientation of crossing α-helices with respect to their respective longitudinal strips. In crossing regions of helices, we looked at circumferential breadth of the hydrophobic strip and the relative frequencies of both small and charged amino acids of that strip in crossing regions between helices. We asked whether the local organization of hydrophobicity or other consensus structures on a longitudinal surface of a helix determines the crossing points of packed helices. For example, small residues in the hydrophobic strip may determine the positions of preferred crossing regions (as do notches in a log), and the hydrophilicity of charged residues may warrant exclusion from these hydrophobic crossing regions.

MATERIALS AND METHODS

For the analysis of the distributions of residues in and near α-helices, sequences of α-helices were used from the paper of Presta and Rose (7) first, and for the remainder of the helices, from the paper of Richardson and Richardson (8). A circular template for a helix with a longitudinal hydrophobic strip was superimposed on each of those helices. The template held 18 symbols: □●△●□○○○□●△●□○○○□●△○. This generic, helical template corresponded to a sheet projection with successive coils of the helix in slanting

* This work was supported by American Cancer Society Grant IM-582 and by the Council at the University of Massachusetts Medical Center for the Molecular Graphics Facility. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

§ Student from Harvard College and undergraduate research fellow of the National Cancer Institute Oncology Education Grant CA39802.

¶ Student from Williams College and undergraduate research fellow of the National Cancer Institute Oncology Education Grant CA39802.

‖ Student from Dartmouth College and undergraduate research fellow of the University of Massachusetts Medical School and subsequently Fuller Fellow of the American Cancer Society, Massachusetts Division.

§§ To whom correspondence should be addressed: Dept. of Pharmacology, University of Massachusetts Medical School, 55 Lake Ave., North, Worcester, MA 01655. Tel.: 508-856-3327; Fax: 508-856-5080.

[1] The abbreviations used are: SOHHI, strip-of-helix hydrophobicity index; LIAD, limiting interhelical alpha-carbon distance.

columns and with longitudinal quadrants in horizontal rows (Fig. 1). By convention, quadrant III had the greatest SOHHI (the mean hydrophobicity in the Kyte-Doolittle scale of amino acids in □ positions). We superimposed the infinite template onto a helical segment 18 times by attaching each of the 18 symbols to the first position in the segment. We chose the overlay which had the maximal SOHHI score. That positioning defined the longitudinal hydrophobic strip (the series of □ positions) and permitted extension of the template into parahelical segments. The distributions of amino acids were determined in each of the template locations within and near the helices.

For the analysis of crossing helices, 15 proteins were studied with the Quanta program of Polygen Corp. on a Silicon Graphics 4D/70 GT computer system. Cα backbone projections were displayed with coordinates and helix lengths from the Brookhaven Protein Data Bank (protein codes: 1ECA, 1LYZ, 1 MBO, 1RHD, 1SBT, 2ACT, 2LDX, 2LZM, 2SNS, 3C2C, 3PGK, 3TLN, 4TNC, 5CPA, 7CAT). Our analysis of 13 pairs of packed helices previously studied by Lesk and Chothia (9) showed that the minimal distances between Cαs of two crossing helices were less than 7.5 Å. For all residues in crossing helices which were no more than 7.5 Å apart, we measured distances from each residue's Cα to the Cαs of neighboring helices. Such measurements were characterized with respect to residues being in □, ●, ○, △, and positions of the strip-of-helix template assignment (1, 2).

Z scores were calculated with respect to empirical distributions of residues across the helices. The *Z* score is (p − observed frequency)/$\sqrt{p(1-p)/n}$, where p is the expected frequency. The expected frequency was based on the empirical distribution of amino acids for all the proteins. In the tables, double-underlined values were significant at $p < 0.001$, single-underlined values were significant at $p < 0.01$, and italicized values were significant at $p < 0.05$. The remaining values indicated were not significant at $p = 0.05$.

RESULTS

Helices terminate when the longitudinal hydrophobic strip is not extended. The assignments of □ positions in some helices and their parahelical segments in cytochrome c_2 are illustrated in Table I. Frequencies of amino acids were determined in □ positions and in intervening loops (○, ●, and △ positions between the □) for 247 helices and their virtual extensions in 55 crystallized proteins (Table II). The virtual extensions were the template assignments in the parahelical regions extending the pattern assigned to the helix itself. The first and second virtual □ positions would have occurred in the longitudinal hydrophobic strip were the helix extended. In the N- and C-terminal □ positions of true helices, the frequencies of Leu, Ile, Val, Phe, or Met substantially exceeded those predicted for an empirical distribution of amino acids for all the proteins ($p < 0.001$). Charged amino acids were suppressed in the terminal □ positions of the true helices. The frequencies of Leu, Ile, Val, Phe, or Met in the first and second □ positions in each virtual extension of the helix fell to the level predicted from the null hypothesis, *i.e.* that the empirical distribution over the entire set of proteins determined the frequencies. The placement of Leu, Ile, Val, or Phe in recurrent positions in the primary sequence determines the formation of an α-helix with a longitudinal strip, when the longitudinal hydrophobic strip can stabilize helical nucleation against a hydrophobic surface (2). This hypothesis implies that the absence of a hydrophobic residue in the extension of that strip fails to anchor the next successive loop and thus dictates termination of the helix. The excess frequency of several amino acids differed significantly at N *versus* C termini of α-helices (Table II). Asp and Glu were increased in frequency in the N-terminal loop of the real helix. Lys and His were increased in the C-terminal loop of the real helix, and Arg and His were increased in the C-terminal first virtual □ position. The distributions of these amino acids otherwise approximated the empirical distribution model for the remainder of the helix, except in □ positions where they were excluded. The negative residues Asp and Glu stabilize the helix N-terminal macrodipole δ+ charge in the native protein (6). The positive residues His, Lys, and Arg stabilize the helix C-terminal macrodipole δ− charge. Asn was also more frequent in the N-terminal loop, forming a hydrogen bond to the peptidyl backbone to initiate the helix (8).

The hydrophobic strip is narrow. While most Leu, Ile, Val, Phe, and Met residues in helices fell in the longitudinal hydrophobic strip with the greatest strip-of-helix hydrophobicity index (2), we examined the distribution of these hydrophobic residues in the remainder of the helix. The residues in the hydrophobic strip do not fall precisely in a straight line (Fig. 1). Some of the positions in quadrants II and IV, the "strip interdigitating positions," fall closely along quadrant III (●). We examined the distribution of Leu, Ile, Val, Phe, and Met in these strip bordering positions of quadrants II and IV and in the remainder of quadrants I, II, and IV (Table III). Leu, Ile, Val, Phe, and Met were restricted to □ and excluded from ● as well as from ○ and △; there was no tendency for broadening of the longitudinal hydrophobic strip. Asp, Glu, and Lys were found in ○ and ▲ positions while His and Arg occurred in ●. Asn was more often in ●; Pro, Gln and Thr, in △; and Tyr in ● but not ○.

A "hydrophobicity break" in the hydrophobic strip-of-helix was defined as the single amino acid in the strip with minimal hydrophobicity. The distributions of amino acids in that

TABLE I

Cytochrome c_2 (3C2)

The strip-of-helix template □ position assignments to helices of eight or more amino acids are indicated with underlining both within the helices and in extensions of the template to surrounding sequences. The amino acid with the smallest side chain in the longitudinal strip-of-helix is indicated (•). In analyses of 55 proteins, the □ positions in the helix were generally Leu, Ile, Val, Phe, or Met, and the first virtual □ positions beyond the helix were not Leu, Ile, Val, Phe, and Met. Positive and negative residues are indicated (+ or −) when they fell in positions where they were found in this study at non-uniform distributions. Asp and Glu were more common in the N terminus loop of the helix, and His, Arg, and Lys were more common in the C-terminal loop of the helix and first C-terminal virtual □. The following interhelical Cα distances were observed: Met^{55}-Ser^{82} 5.03 Å; Ser^{51}-Ser^{82} 6.05 Å; Glu^{64}-Ser^{82} 5.64 Å; Leu^{67}-Ile^{105} 7.17 Å.

Helix	N virtual	True	C virtual
3–11	E G	D A A A G E K V S	K K C L A
50–58	N Y A Y S	E S Y T E M K A K	G L T W T
63–83	K G L T W	T E A N L A A Y V K N P K A F V L E K S G	E P K A K
97–109	T F K L T	K D D E I E N V I A Y L K	T L K

TABLE II

Distribution of amino acids in the longitudinal hydrophobic strip □ and in intervening loops (○, ●, and △) in 252 α-helices (real) and in parahelical segments extended in virtual helical configurations (virtual)

	N Terminus			C Terminus		
	Virtual Strip*	Real		Real		Virtual strip
		Loop	Strip	Strip	Loop	
L		−2.1	+5.0	+9.6	−2.6	
I		−2.4	+4.2	+5.5	−3.0	
V		−3.0	+4.1	+5.6	−4.1	
F		−3.1	+2.5	+4.1	−2.8	−2.8
M		−2.2	+2.2	+3.1		
D		+4.9		−3.3		
E		+4.1		−3.3		
H				+2.0	+2.0	
R			−2.9	−2.6		+2.9
K			−2.9	−3.2	+4.5	+2.4
A						
C						
G						
N		+2.1		−3.1		
P				−3.2		
Q				−2.8	+2.1	
S				−2.1		
T		−2.2		−2.5		
W						
Y						

* The distributions of amino acids in the first proximal virtual loop and second proximal virtual strip in both N- and C-terminal parahelical segments were uniformly at the frequency of the uniform distribution of amino acids in proteins and were not reported in this table.

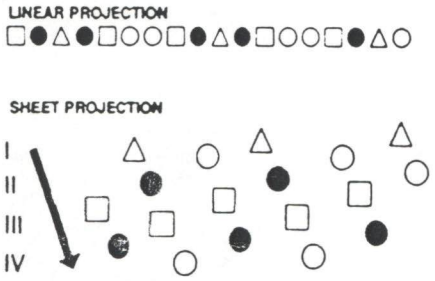

FIG. 1. **Sheet projection of linear template for an α-helix with a longitudinal hydrophobic strip.** □, hydrophobic positions in quadrant III; △, nonhydrophobic residues of quadrant I; ●, nonhydrophobic positions in quadrants II and IV interdigitating with quadrant III; ○, nonhydrophobic positions in quadrants II and IV farther from the median of quadrant III. This template was applied to helical segments to maximize the mean hydrophobicity of residues in □ positions.

position, and in the adjacent ($n-2$, $n-1$, $n+1$, $n+2$) positions along the longitudinal hydrophobic strip were scored (Table IV). His, Asn, and Trp were frequently present in the "break" and both positions in the longitudinal hydrophobic strip adjacent to the break held increased frequencies of Leu, Ile, Val, and Phe (each, $p < 0.001$) and Met ($p < 0.01$). We conclude that longitudinal hydrophobic strip-of-helix sequences can be interrupted by a single nonhydrophobic residue. We suggest that two successive non-(Leu, Ile, Val, Phe, or Met) residues in the strip-of-helix terminate the helix. This observation may help to locate helix termini by searching for a motif of hydrophobic residues occurring in terminal □ but not in the two, next virtual □ positions in the extension of the longitudinal hydrophobic strip.

TABLE III

Longitudinal distributions of amino acids in α-helices

	□	●	○	△
L	+12.9	−4.1	−4.4	−5.5
I	+10.0	−4.0	−2.8	−3.9
V	+9.7	−3.4	−3.2	−3.9
F	+8.2		−3.6	−3.6
M	+3.7			
D	−5.3		+4.1	
E	−6.1		+2.3	+3.0
H		+3.0		
K	−7.1		+2.6	+4.4
R	−5.1	+3.3		
A				
C	+2.2			
G	−2.4			
N	−5.1		+3.1	
P	−3.0			+2.3
Q	−4.8			+2.2
S	−2.5			
T	−2.8			+3.5
W				
Y		+4.7		

TABLE IV

Distributions of amino acids in □ positions of a longitudinal hydrophobic strip centered on the least hydrophobic residue

The longitudinal hydrophobic strips of 247 helices were aligned on the least hydrophobic residue other than Leu, Ile, Val, Phe or Met. Within the longitudinal hydrophobic strip, amino acids in the positions adjacent to the least hydrophobic residue were usually Leu, Ile, Val, Phe, or Met.

	−2	−1	Break	+1	+2
L	+4.8	+4.8	0	+7.0	+6.4
I	+4.8	+5.2	0	+6.7	+3.9
V	+3.7	+3.9	0	+5.1	+4.5
F		+2.9	0	+2.1	+5.9
M		+2.2	0		
D		−2.2		−2.7	−2.3
E		−2.5		−2.3	−2.6
H			+3.9		
K	−2.1	+2.7		−3.3	−2.8
R				−2.2	
A					
C		+2.1		+2.5	
G					
N			−2.4	−2.2	
P					
Q				−2.2	
S				−2.6	
T					−2.1
W			+2.2		
Y					

We examined the three-dimensional orientations of neighboring α-helices in a series of proteins in terms of the proximity of longitudinal hydrophobic strips and of Cα distances between pairs of helices. A variety of models have been offered

for such helical packing (9–14). A general view is that proteins pack to bring together hydrophobic surfaces of α-helices, β-sheets, or other local structures in a hydrophobic core (3, 15–17). The resultant solvent shielding for hydrophobic residues contributes to overall energy stabilization (18). Protein folding has been interpreted to maximize solvent inaccessibility for hydrophobic amino acids (19, 20). We have extended such hydrophobicity-based analyses to test the extent to which crossing of α-helices correlates with features in and around the longitudinal hydrophobic strip of those α-helices.

A crossing region was defined. Two α-helices were defined as crossing if there was at least one pair of Cαs whose interhelical distance was less than 7.5 Å. We called such a measurement the Limiting Interhelical α-Carbon Distance (LIAD). In parallel to the method of Chothia *et al.* (13) to measure multiple residue interactions at the closest point of approach between the two helices, we determined the three shortest LIADs without restricting their lengths as long as the shortest was less than 7.5 Å. The pair of amino acids determining a LIAD was called the LIAD pair. Individual amino acids in a helix could occur in more than one LIAD pair. The crossing region was defined to include those amino acids on one helix in the shortest three LIAD pairs. The magnitude of the LIAD is not correlated with the residue volumes of the amino acids forming the shortest LIAD (correlation $r = 0.44$). Single loop helices or helices with LIAD pairs involving only the terminal 2 residues were excluded because they usually only approached but did not cross another helix. 86 helices in 15 proteins had 74 pairs of adjacent α-helices with crossing regions.

The rotational orientation between α-helices was determined with respect to crossing longitudinal hydrophobic strips. Amino acids in crossing regions frequently also lay in longitudinal hydrophobic strips ($Z = +5.1$, $p < 0.001$). We tested the frequency with which longitudinal hydrophobic strips in neighboring helices intersected each other, *i.e.* the helices crossed through their longitudinal hydrophobic strips (Table V). Crossing between hydrophobic strips occurred when at least one LIAD, termed the strip-to-strip LIAD, had both amino acids of the LIAD pair in hydrophobic strips of their respective helices (Table V). We conclude that longitudinal hydrophobic strips-of-helix frequently face each other.

The crossing of hydrophobic strips on α-helices may be viewed to either contribute to or be derived from the formation of the hydrophobic core. Hydrophobic strips may orient α-helices to create the hydrophobic core of the protein, but crossings may just as well reflect a limiting effect of protein volume. The nonpolar sides of α-helices turn to the inside of the protein in order to minimize their exposure to solvent and are thus more likely to cross each other in smaller than in larger proteins. A weak correlation was found between the percentage of crossing α-helices and size of the protein ($r = 0.57$).

Several amino acids were significantly included in or restricted from crossing regions (Table VI). Hydrophobic amino acids Leu, Ile, Val, Phe, and Met as a group occurred more frequently in crossing regions ($Z = +6.4$, $p < 0.001$). In contrast, both negatively charged amino acids Asp and Glu ($Z = -4.2$) and positively charged amino acids His, Lys, and Arg ($Z = -4.4$) were excluded from crossing regions (each set, $p < 0.001$). The individual amino acids most often included in crossing regions were Val and Ile (each, $p < 0.001$); Ala was significant as well ($p < 0.01$). For the charged amino acids, Lys and Asp were the most highly excluded (each, $p < 0.001$). Excepting His, Thr, and Cys, our distributions did not differ significantly from those of Chothia *et al.* (13).

TABLE V

Distributions of amino acids in crossing regions of α-helices

Distributions of amino acids were calculated in crossing regions defined by the shortest three LIADs between helices when at least one LIAD was less than 7.5 Å. 452 residues in 74 crossing regions were counted, including a fourth LIAD for four crossing regions which had two pairs of amino acids tying for third closest LIAD. The expected percentages were calculated from the distribution of 3661 amino acids in 257 α-helices. z scores were also computed from the data of Chothia *et al.* (13). For groups of amino acids z scores were: L I V F M, +6.3; R K H, −4.4; D E, −4.2.

	No. observed	% observed	% expected	z (here)	z (Chothia)
L	53	11.7	9.6		
I	47	10.4	4.8	+5.7	+4.0
V	54	11.9	6.6	+4.6	+4.0
F	21	4.6	4.8		
M	14	3.1	2.5		
D	10	2.2	6.2	−3.5	−2.2
D	22	4.9	7.6	−2.2	−3.3
H	4	0.9	2.7	−2.4	+2.1
R	16	3.5	3.6		
K	13	2.9	8.2	−4.2	−2.6
A	71	15.7	11.5	+2.9	
C	7	1.5	2.1		−5.1
G	31	6.9	4.9		
N	11	2.4	3.9		
P	10	2.2	2.3		
Q	11	2.4	3.7		
S	27	6.0	5.7		
T	10	2.2	4.9	−2.6	
W	6	1.3	1.3		
Y	14	3.1	2.9		

The distributions of charged amino acids in the longitudinal hydrophobic strip was determined with respect to occurrence in crossing regions. 92% of Asp, Glu, His, Lys, and Arg in such strips did not fall in a crossing region (χ^2 for equal proportions = 6.8; $p < 0.01$). We also determined the smallest amino acid, the "size break," in each longitudinal hydrophobic strip (Table VI). Chothia *et al.* (13) reported packing of smaller amino acids along larger ones at helical crossings. In our analysis, the smallest residue in the strip fell in the crossing region 46% of the time, and 59% of the crossing regions with a strip-to-strip LIAD pair contained at least one size break. Overall, 49% of the smallest amino acids in all longitudinal hydrophobic strips fell in crossing regions ($\chi^2 = 4.8$, $p < 0.05$). We did not find, within crossing regions, any broadening of hydrophobicity around the longitudinal hydrophobic strip. The frequencies of hydrophobic residues and crossing regions involving strip interdigitating ● positions were tested. There was no increase in the frequency of Leu, Ile, Val, Phe, or Met in ● positions which occurred in crossing regions *versus* positions not in crossing regions ($\chi^2 = 0.5$, $p > 0.05$).

DISCUSSION

Since extent of α-helices correlated so closely with termination of the longitudinal hydrophobic strips ($p < 0.001$), we conclude that the anchoring of successive loops of a helix, by hydrophobic residues in the longitudinal hydrophobic strip to another hydrophobic region of a protein, is a significant determinant of helix formation. Peptidyl backbone hydrogen bonding between loops leads to helical geometry and to stability, as does helix macrodipole stabilization by N-terminal

TABLE VI

Distribution of amino acids in □ positions at and adjacent to size breaks within the longitudinal hydrophobic strips of crossing helices

The 86 longitudinal hydrophobic strips were aligned on the residue with the smallest volume on the scale of Chothia (21). When identical amino acids were smallest, the selected amino acid was the one with the largest neighbors. The two most frequently smallest amino acids were Ala and Val (each $p < 0.001$). Within the longitudinal hydrophobic strip the positions next to the size breaks usually had Leu, Ile, Val, Phe, or Met.

	−1	Break	+1
L	+4.2		+2.9
I	+4.9		+5.8
V	+4.2	+4.5	+3.4
F		−2.1	+3.4
M	+3.3		
D			−2.1
E	−2.1		−2.3
H			
R		−2.8	−2.1
K			
A	−2.1	+6.5	
C			
G			
N			
P			
Q			
S			
T			
W			
Y			

Asp, Glu and C-terminal His, Lys, Arg, and transverse hydrogen bonds determined by Asn and Pro. We found that Asp and Glu at the N terminus were restricted to the N-terminal loop of the helix, and Arg, His, and Lys were in the C-terminal loop and first virtual □. Restricted longitudinal distributions of Asn, Glu, Pro, Thr, and Tyr in nonhydrophobic longitudinal quadrants were found. We also found that the longitudinal hydrophobic strips of two adjacent helices frequently crossed each other ($p < 0.001$). The hydrophobic strip was shown to be a narrowly defined region along one longitudinal quadrant of an α-helix. There was no preference for crossing regions or hydrophobicity to extend to ● positions outside the narrowly defined strip-of-helix. The smallest amino acid in a longitudinal hydrophobic strip was frequently found in a helical crossing region ($p < 0.05$), and charged amino acids were excluded from that location ($p < 0.001$). These data support the view that local structures on the surface of an α-helix can influence how such helices will orient to each other in rotation about and translation along the helical axes. This analysis is part of the larger question of the close packing of side chains in the interior of globular proteins (22). The methods of this study complement other models of helical packing.

Our observations of the restricted placements of residues in and about the longitudinal hydrophobic strip may be used to improve methods to predict α-helix formation. The prediction of helices in proteins may be confounded by controlling interactions with other regions of the proteins. On the other hand, prediction of helices in excised fragments of antigenic proteins may well define scavenger sites which dictate the selection and transfer of such peptides to major histocompatibility complex antigen-binding sites (23).

This general method of analysis, based first on a consensus pattern of hydrophobicity, may also be applied to the study of β-sheets and turns. The regulating principle may be the generation of a local structure with a hydrophobic surface containing multiple hydrophobic residues which are adjacent in the folded structure but separated in the primary sequence *in patterns which may form characteristic motifs*. The strength of the local, secondary structure may be reflected in the mean hydrophobicity of the residues in the motif of the hydrophobic surface. For example, hydrophobic residues in particular patterns around prolines may characterize some β-turns and the alternating hydrophobicity of β-strands can be identified (24, 25). The principles of this study may also be used to predict docking of secondary structural elements to form tertiary structures in proteins.

Acknowledgment—We thank Patricia J. Downe for typing the manuscript.

REFERENCES

1. Reyes, V. E., Phillips, L., Humphreys, R. E., and Lew, R. A. (1989) *J. Biol. Chem.* **264**, 12854-12858
2. Torgerson, R. R., Lew, R. A., Reyes, V. E., Hardy, L., and Humphreys, R. E. (1991) *J. Biol. Chem.* **266**, 5521-5524
3. Perutz, M. F., Kendrew, J. C., and Watson, H. C. (1965) *J. Mol. Biol.* **13**, 669-678
4. Schiffer, M., and Edmundson, A. B. (1967) *Biophys. J.* **7**, 121-135
5. Kaiser, E. T., and Taylor, J. W. (1987) *Methods Enzymol.* **154**, 473-487
6. Hol, W. G. J., Halie, L. M., and Sander, D. (1981) *Nature* **294**, 532-536
7. Presta, L. G., and Rose, G. D. (1988) *Science* **240**, 1632-1641
8. Richardson, J. S., and Richardson, D. C. (1988) *Science* **240**, 1648-1652
9. Lesk, A. M., and Chothia, C. (1980) *J. Mol. Biol.* **136**, 225-270
10. Crick, F. H. C. (1953) *Acta Crystallogr.* **6**, 689-697
11. Richmond, T. J., and Richards, F. M. (1978) *J. Mol. Biol.* **119**, 537-555
12. Efimov, A. V. (1979) *J. Mol. Biol.* **134**, 23-40
13. Chothia, C., Levitt, M., and Richardson, D. (1981) *J. Mol. Biol.* **145**, 215-250
14. Chou, K., Nemethy, G., and Scheraga, H. A. (1983) *J. Phys. Chem.* **87**, 2869-2881
15. Kellis J. T., Jr., Nyberg, K., and Fersht, A. R. (1989) *Biochemistry* **28**, 4914-4922
16. Bowie, J. U., Clarke, N. D., Pabo, C. O., and Sauer, R. T. (1990) *Proteins* **7**, 257-264
17. Matouschek, A., Kellis, J. T., Jr., Serrano, L., Bycroft, M., and Fersht, A. R. (1990) *Nature* **346**, 440-445
18. Lim, W. A., and Sauer, R. T. (1989) *Nature* **339**, 31-36
19. Bowie, J. U., Reidhaar-Olson, J. F., Lim, W. A., and Sauer, R. T. (1990) *Science* **247**, 1306-1310
20. Bowie, J. U., Lüthy, R., and Eisenberg, D. (1991) *Science* **253**, 164-170
21. Chothia, C. (1975) *Nature* **254**, 304-308
22. Ponder, J. W., and Richards, F. M. (1987) *J. Mol. Biol.* **193**, 775-791
23. Lu, S., Reyes, V. E., Bositis, C. M., Goldschmidt, T. G., Lam, V., Torgerson, R. R., Ciardelli, T., Hardy, L., Lew, R. A., and Humphreys, R. E. (1992) *Vaccine* **10**, 3-9
24. Osterman, D. G., and Kaiser, E. T. (1985) *J. Cell. Biochem.* **29**, 57-72
25. Minakata, H., Taylor, J. W., Walker, M. W., Miller, R. J., and Kaiser, E. T. (1989) *J. Biol. Chem.* **264**, 7907-7913