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TO: DR. D.A. BROMLEY

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SUBJECT: HE IS WRITING SUGGESTING THAT DR. BROMLEY AND THE
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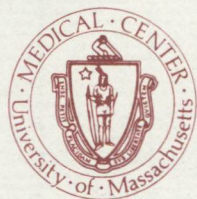
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June 11, 1992

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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.

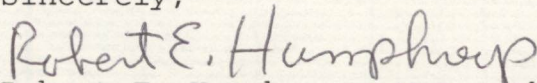
Among the series of issues you and your colleagues need to address, please do look carefully at the needs of the excellent state schools and small to medium size biotech companies. Generally, we do not have the resources in legal departments, administrative depth and capital as do the great institutions 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,

A handwritten signature in dark ink, reading "Robert E. Humphreys". The signature is written in a cursive style with a large, prominent "H".

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

Residues in the Longitudinal, Hydrophobic Strip-of-helix Relate to Terminations and Crossings of α -Helices*

(Received for publication, November 1, 1991)

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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 ($\square \circ \circ \circ \square \circ \circ \square \circ \circ \circ \square \circ \circ \circ$) was fitted to maximize the mean hydrophobicity of $\square$ 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 $\square$ positions in the longitudinal strip-of-helix at an increased frequency ($p < 0.001$), but in the first and second $\square$ 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 $\square \circ \circ \circ \square \circ \circ \square \circ \circ \circ$

$\square \circ \circ \circ \square \circ \circ \circ$ to maximize the strip-of-helix hydrophobicity index (SOHHI,¹ the mean hydrophobicity of residues in $\square$ position in the template (1, 2)). In helices of crystallized proteins such $\square$ positions were usually aligned along the surface of the helix in a longitudinal strip (2). Such $\square$ 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 $\square$ 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: $\square \bullet \Delta \bullet \square \circ \circ \square \bullet \Delta \bullet \square \circ \circ \square \bullet \Delta \bullet \square \circ \circ$. 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.

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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 $\square$ 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 $\square$ 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. α 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 C α s 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 C α to the C α s of neighboring helices. Such measurements were characterized with respect to residues being in $\square$, $\bullet$, $\circ$, Δ , 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 $(p - \text{observed frequency}) / \sqrt{p(1-p)/n}$, 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 $\square$ positions in some helices and their parahelical segments in cytochrome c_2 are illustrated in Table I. Frequencies of amino acids were determined in $\square$ positions and in intervening loops ($\circ$, $\bullet$, and Δ positions between the $\square$) 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 $\square$ positions would have occurred in the longitudinal hydrophobic strip were the helix extended. In the N- and C-terminal $\square$ 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 $\square$ positions of the true helices.

The frequencies of Leu, Ile, Val, Phe, or Met in the first and second $\square$ 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 $\square$ position. The distributions of these amino acids otherwise approximated the empirical distribution model for the remainder of the helix, except in $\square$ positions where they were excluded. The negative residues Asp and Glu stabilize the helix N-terminal macrodipole $\delta+$ charge in the native protein (6). The positive residues His, Lys, and Arg stabilize the helix C-terminal macrodipole $\delta-$ 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 ($\bullet$). 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 $\square$ and excluded from $\bullet$ as well as from $\circ$ and Δ ; there was no tendency for broadening of the longitudinal hydrophobic strip. Asp, Glu, and Lys were found in $\circ$ and Δ positions while His and Arg occurred in $\bullet$. Asn was more often in $\bullet$; Pro, Gln and Thr, in Δ ; and Tyr in $\bullet$ but not $\circ$.

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 $\square$ 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 $\square$ positions in the helix were generally Leu, Ile, Val, Phe, or Met, and the first virtual $\square$ 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 $\square$. The following interhelical Ca distances were observed: Met⁵⁵-Ser⁶² 5.03 Å; Ser⁵¹-Ser⁶² 6.05 Å; Glu⁶⁴-Ser⁶² 5.64 Å; Leu⁶⁷-Ile¹⁰⁶ 7.17 Å.

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

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		Virtual strip	
		Loop	Strip		
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
M		-2.2	+2.2	+3.1	
D		+4.9		-3.3	
E		+4.1		-3.3	
H				+2.0	
R			-2.9	-2.6	+2.9
K			-2.9	-3.2	+4.5
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.

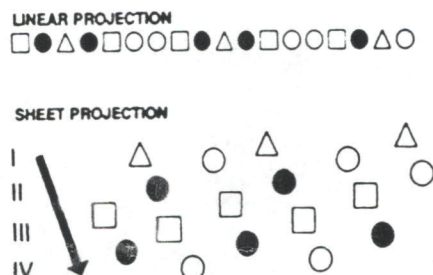


FIG. 1. Sheet projection of linear template for an α -helix with a longitudinal hydrophobic strip. □, hydrophobic positions in quadrant III; △, nonhydrophobic residues of quadrant I; ●, nonhydrophobic positions in quadrants II and IV interdigitating with quadrant III; ○, nonhydrophobic positions in quadrants 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

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					

not in the two, next virtual □ positions in the extension of the longitudinal hydrophobic strip.

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 Ca 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 C α s 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	<u>+5.7</u>	<u>+4.0</u>
V	54	11.9	6.6	<u>+4.6</u>	<u>+4.0</u>
F	21	4.6	4.8		
M	14	3.1	2.5		
D	10	2.2	6.2	<u>-3.5</u>	-2.2
D	22	4.9	7.6	<u>-2.2</u>	<u>-3.3</u>
H	4	0.9	2.7	-2.4	+2.1
R	16	3.5	3.6		
K	13	2.9	8.2	<u>-4.2</u>	-2.6
A	71	15.7	11.5	+2.9	
C	7	1.5	2.1		<u>-5.1</u>
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 $\bullet$ positions were tested. There was no increase in the frequency of Leu, Ile, Val, Phe, or Met in $\bullet$ 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 $\square$ 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	<u>+4.2</u>		<u>+2.9</u>
I	<u>+4.9</u>		<u>+5.8</u>
V	<u>+4.2</u>	<u>+4.5</u>	<u>+3.4</u>
F		-2.1	<u>+3.4</u>
M	<u>+3.3</u>		
D			-2.1
E	-2.1		-2.3
H			
R		-2.8	-2.1
K			
A	-2.1	<u>+6.5</u>	
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 $\square$. 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 $\bullet$ 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.

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"Document Control for Division of Life Sciences"

TYPE: ACTION DOCUMENT NUMBER: 9202215
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

FROM: BLAIR, William McCormack Mrs.

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 06/11/92

SUBJECT: SHE IS FORWARDING INFORMATION REGARDING THE NATIONAL
CANCER INSTITUTE GRAND ROUNDS.

DIRECTORATE STAFF
ASSIGNED: LIFE SCIENCES ASSIGNED: D.A. Henderson

ACTION STAFF
REQUIRED: AS APPROPRIATE ACTION: DRAFT FOR DAB

SENDER'S DUE DATE:
OSTP DUE DATE: 06/24/92 STAFF DUE DATE 06/24/92
DATE COMPLETED: DATE COMPLETED/DEPT: 06/22/92

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #: CONTACT PERSON:
REMARKS: PHONE: EXT:

OSTP RECEIVED: 06/17/92
FILE: P-LIFE SCIENCES

DEPT RECEIVED: 06/19/92

CENTRAL FILES:



2215
2510 FOXHALL ROAD
WASHINGTON, D. C. 20007

June 11, 1992

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

Dear Allan,

We have been out of communication for some time, which I deeply regret and hope that soon that might be remedied.

I wanted to bring to your attention what will be an exceptionally interesting National Cancer Institute Grand Rounds on June 24th. Dr. Myron Essex will be discussing three very exciting new approaches in their AIDS research program. As you are aware, this is a very creative, innovative and productive lab.

- Enhancement of CTL Response in HIV Infected Individuals by IL7 - a Therapy Approach
- VPX gene of SIV/HIV-2 Inhibition of Replication of HIV-1 - a Genetic Therapy Approach
- Nonrandom Distribution of gp120 N-linked Glycosylation Sites Important for Infectivity of HIV-1 - a Vaccine Approach

I serve as an Advisor to this Department of Cancer Biology at Harvard and we are really very

excited about some of these recent lab results. A very promising process for making an AIDS vaccine

seems to be unfolding - it involves the selective genetic removal of "sugar attachment sites" on the virus surface molecule. A serious problem with earlier versions of experimental HIV vaccines has been the massive "sugar coating" that covers the molecule, which usually resulted in a lack of adequate immune stimulation.

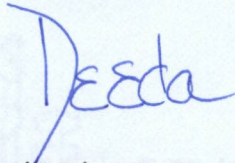
It has been a long term goal to come up with a vaccine that could be available at a reasonable cost to our nation's minority groups and most especially populations in developing countries. It now appears that we have a fresh new way to approach the vaccine problem. If it works, it is even possible to dream that it could provide a new approach for making vaccines for various infections that present similar problems, ranging from malaria to Lyme disease. This is another example of how AIDS research can provide benefits for other medical problems.

I feel that the White House has been virtually silent for the last decade on the subject of AIDS - occasional photo opportunities but a real commitment certainly has not been evident. The initiatives for AIDS funding have come from the Senate and Congress - not from the White House. Perhaps if you conceivably might be interested - if you were to hear firsthand of these advances - you might be able to make an impact on the Oval Office.

Page 3

At any rate, I think you would find it a very interesting scientific talk.

All the best,

A handwritten signature in blue ink, appearing to read "Deeda". The signature is written in a cursive style with a large initial "D" and a long horizontal stroke extending to the right.

Mrs. William McCormick Blair, Jr.

NATIONAL CANCER INSTITUTE
CLINICAL ONCOLOGY PROGRAM
COMBINED ROUNDS
ACRF AMPHITHEATER, 1ST FLOOR
WEDNESDAY, 8:30 A.M.

JUNE 24, 1992

NEW APPROACHES TO AIDS -
THERAPY AND VACCINES

MYRON E. ESSEX, D.V.M., PH.D.
DIRECTOR
DEPT. OF CANCER BIOLOGY
HARVARD SCHOOL OF PUBLIC HEALTH

THE WHITE HOUSE

WASHINGTON

June 22, 1992


Dear Mrs. Blair:

I was delighted to hear from you again and to learn of the promising new developments with regard to HIV treatment and prevention. Dr. Essex and his colleagues are a most creative and productive group indeed.

I would agree with you that developments in the production of an effective and inexpensive vaccine which can be utilized globally are of special importance. Given the problems in effecting behavioral change and the inherent difficulties in developing effective anti-virus compounds, an approach grounded in prevention vaccination is one which deserves special emphasis.

As I am sure you know, NIH, Walter Reed and a number of private sector companies are investing substantial and increasing funds in HIV vaccine development. The results, as I have reviewed them, are at least cautiously encouraging. To assure that development proceed as expeditiously as possible, you should know that I have created a special working group under the Federal Coordinating Council for Science, Engineering and Technology to develop a coordinated plan for vaccine testing. That group expects to complete its work later this year.

Dr. D. A. Henderson is my Associate Director for Life Sciences and I can assure you he is keeping in close touch with developments in this important field.

Many thanks for your letter.

Sincerely yours,



D. Allan Bromley

The Assistant to the President
for
Science and Technology

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

OSTP STAFFING SHEET

SUBJECT: Correspondence for Dr. Bromley's Signature

ORIGINATOR: D.A. Henderson PHONE 2892

DATE ORIGINATED: 6/22/92 DATE DUE: 6/24/92 CORR TRACKING NO: 9202215

EXTERNAL COORDINATION: _____

		COMMENTS	DATE
3	DIRECTOR	Signature	
2	CHIEF OF STAFF	Clear	
	GENERAL COUNSEL		
	EXEC. ASST.		

ACTION REQUESTED:

PLEASE RETURN TO ROOM 494 AFTER SIGNATURE FOR DUPLICATING AND DISTRIBUTION.

[illegible]

"Document Control for Division of Life Sciences"

TYPE: Action Item

DOCUMENT NUMBER: 9202126

ORIGINATOR: 02

STATUS I

DIRECTORATE STATUS C

FROM: BANTAN, Jan; Bantan Properties

TO: D.Allan Bromley

DATE OF
CORRESPONDENCE: 06/04/92

SUBJECT: THEY ARE WRITING TO ASK DR. BROMLEY'S SUPPORT IN
KEEPING THE FAST FLUX TEST FACILITY, HARTFORD, OPEN.

DIRECTORATE

STAFF

ASSIGNED: LIFE SCIENCES

ASSIGNED: William Raub

ACTION

STAFF

REQUIRED: AS NECESSARY

ACTION: Necessary Action

SENDER'S DUE DATE:

OSTP DUE DATE: 06/25/92

STAFF DUE DATE 06/25/92

DATE COMPLETED:

DATE COMPLETED/DEPT: 07/29/92

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #:

CONTACT PERSON:

PHONE:

EXT:

REMARKS: 7/9, per Mary, action has been extended for 2wks. System
crashed, item extended for as long as necessary.dic



OSTP RECEIVED: 06/04/92
FILE: P-LIFE SCIENCES

DEPT RECEIVED: 06/11/92



CENTRAL FILES:

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

July 29, 1992

Dear Jan Bantan:

I am responding to your letter to Dr. D. Allan Bromley in which you urge support for continued funding for the Fast Flux Test Facility (FFTF) in Hanford.

Many of us share your interest in ensuring ready availability of isotopes for nuclear medicine and other purposes. The FFTF is one of several facilities that have yielded medically important results as a byproduct of their focus on one or another aspect of nuclear physics. As needs change in the latter area, as is inevitable, and the Department of Energy (DoE) makes the requisite adjustments in its spending plans, the Office of Science and Technology Policy is working with DoE and other agencies to determine how best to avert the prospective isotope shortages that loom on the horizon. The overall problem is extraordinarily complex, and nothing short of complementary efforts by private industry and government seems to have a reasonable chance of succeeding.

With respect specifically to the FFTF, its continued operation does not claim as high a priority as do other DoE activities. Therefore, the budget request for Fiscal Year 1993, which begins on October 1, included funds for either the federal government's share of the operating costs (if Washington State were successful in attracting a significant amount of non-DoE funding) or the costs of placing the facility in a non-active status (if the State were unsuccessful). To date, the State has not attracted the requisite support, and the prospects do not seem promising. The reactor therefore is being maintained in "hot standby" mode pending further decisions about its future.

I recognize that these facts only will exacerbate your concerns. However, in view of the many competing demands upon the resources of DoE, we must address the isotope-supply issue for nuclear medicine and other areas within such constraints.

Sincerely yours,



William F. Raub, Ph.D.
Special Assistant for Health Affairs

Jan Bantan
Bantan Properties
5-A N. Tweedt St.
Kennewick, WA 99336

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

July 29, 1992

Dear Jan Bantan:

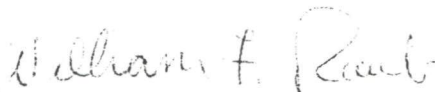
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I recognize that these facts only will exacerbate your concerns. However, in view of the many competing demands upon the resources of DoE, we must address the isotope-supply issue for nuclear medicine and other areas within such constraints.

Sincerely yours,



William F. Raub, Ph.D.
Special Assistant for Health Affairs

Jan Bantan
Bantan Properties
5-A N. Tweedt St.
Kennewick, WA 99336

"Document Control"

TYPE: ACTION

DOCUMENT NUMBER: 9202126

ORIGINATOR: 02

STATUS I

DIRECTORATE STATUS

FROM: BANTAN, Jan: BANTAN PROPERTIES

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 06/04/92

SUBJECT: THEY ARE WRITING TO ASK DR. BROMLEY'S SUPPORT IN
KEEPING THE FAST FLUX TEST FACILITY, HARTFORD, OPEN.

DIRECTORATE STAFF
ASSIGNED: LIFE SCIENCES ASSIGNED:

ACTION STAFF
REQUIRED: AS NECESSARY ACTION:

SENDER'S DUE DATE:
OSTP DUE DATE: 06/25/92 STAFF DUE DATE
DATE COMPLETED: DATE COMPLETED/DEPT:

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #: CONTACT PERSON:
REMARKS: PHONE: EXT:

OSTP RECEIVED: 06/11/92
FILE: P-LIFE SCIENCES

DEPT RECEIVED:

CENTRAL FILES:

RECEIVED

92 JUN 11 P 2: 23

OSTP
MAIL ROOM**Banton Properties**

5-A N. Tweedt St.
Kennewick, Wa 99336
(509)735-7268

Dr. D. A. Bromley
Exec. Office of the President
OSTP
Washington, DC 20506

June 4th, 1992

Re: Fast Flux Test Facility/Hanford

Dear Dr. Bromley,

When the FFTF began full-power operation at Hanford in 1982, its sole purpose was to test fuels, materials and components for advanced nuclear systems. Since that time, the FFTF has branched out into many other scientific arenas.

There is growing recognition nationwide that the Fast Flux Test Facility has broad capabilities in a field which is just beginning to open up - nuclear medicine.

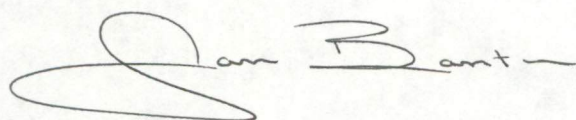
Since 1987, FFTF has produced isotopes for the medical community. The first isotope successfully produced and sold commercially was Gadolinium 153, used in osteoporosis detection and diagnosis.

Since then, the reactor has distinguished itself as a source of over 60 isotopes, mostly for medical use. With these isotopes, nuclear medicine is developing new treatments that will benefit premature babies, pain sufferers, tumor victims and others.

The isotopes produced in the reactor will save lives. Only FFTF can produce the quality and quantity that will be needed for many of the future developments in the nuclear medicine field.

Dr. Bromley, your support for FFTF is very much needed. FFTF is recognized as the most advanced and versatile test reactor in the world and has established itself in the scientific community as a valuable tool. I urge you, please give this issue proper consideration, and assist with FFTF remaining open, thus allowing research in nuclear medicine to continue to grow.

Thank you

A handwritten signature in dark ink, appearing to read "Jan Barton". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Jan Barton
Barton Properties

Jim Keenan

DOE

7/28/92

NE (DOE) requested

Reckland place

FFTF in

"Not standby" 400° F.

control rods removed in core

mechanisms re disconnected

unit is inert

Circulation pump

875-⁺~~400~~ m

Work unsuccessful re
fuel vanning - vs, Germany, AT

DEPARTMENT OF ENERGY
FY 1993 CONGRESSIONAL BUDGET REQUEST
ENERGY SUPPLY, RESEARCH AND DEVELOPMENT

OVERVIEW

WASTE MANAGEMENT (NON-DEFENSE)

The goal of the Waste Management Program is to provide safe, environmentally sound and cost-effective treatment, storage, transport and disposal of waste resulting from activities of the non-defense energy supply, research and development programs in the Department of Energy and to coordinate activities for managing certain civilian wastes. It includes the general waste management for low-level waste (LLW), hazardous waste and transuranic waste (TRU), as well as management of the West Valley Demonstration Project, the DOE Waste Minimization Program, the National Low-Level Radioactive Waste Program and the Fast Flux Test Facility which was added by Congress to the FY 1991 and FY 1992 Waste Management appropriation.

The focus of non-defense management activities is to provide a complete waste management program including characterization, packaging, transportation, treatment, storage, disposal, and waste minimization resulting in less waste to dispose of and less impact on the environment. Improved characterization of low-level waste (LLW) is being implemented to identify the mixed waste portion so that only radioactive waste or mixed waste is managed in the appropriate facilities. Storage of LLW occurs while sites complete actions to meet waste treatment and disposal criteria established by DOE Orders and, for mixed LLW, regulatory requirements based on the Resource Conservation and Recovery Act (RCRA).

The focus of the hazardous waste management program is to effectively manage hazardous waste and the hazardous portion of mixed waste in compliance with the RCRA, Toxic Substance Control Act (TSCA), the Clean Water Act (CWA), and other Federal, State and local regulations. The management strategy for hazardous waste includes 1) avoidance of hazardous waste generation, 2) providing treatment capacity to treat waste as it is generated to minimize storage requirements, 3) use of best available treatment technology, and 4) RCRA compliant disposal.

This request funds activities necessary to meet milestones and legal requirements included in compliance agreements, consent orders, and Federal and State statutes and regulations and provides for implementation of all DOE Orders and highest priority discretionary activities which include reducing risk to the environment, safety and health.

LOW-LEVEL WASTE (LLW)

The goal of the National LLW Program is to facilitate the establishment of a reliable nationwide system for management of commercially generated low-level radioactive waste by implementing responsibilities assigned to DOE under P.L. 99-240, "Title I Low-Level Radioactive Waste Policy Amendments Act of 1985." The Act assigned to States the responsibility for providing, either individually or in cooperation with other States, disposal of LLW generated within their borders. Responsibilities assigned to DOE by the Act include technical and financial assistance to compacts and States in meeting their responsibilities, annual reporting to the Congress on progress being made by States on low-level waste management in the U.S., certain administrative and financial functions, and disposal of greater-than-class C LLW resulting from activities of licensed generators, and disposal of LLW owned or generated by DOE.

FAST FLUX TEST FACILITY (FFTF)

The FFTF is operated by the Department at the Hanford, Washington site. The FY 1991 appropriation included this program under the Office of Environmental Restoration and Waste Management (EM) account. FY 1992 funding for FFTF operation is also provided in the EM account with FY 1992 Energy and Water Appropriation Act. The State of Washington, with DOE support, is leading an effort to obtain non-DOE funding support for the continued operation of the FFTF. If this marketing effort is not successful by March 31, 1992, FY 1992 funding will be used to fund shutdown of the facility. The requested FY 1993 funding provides for shutdown activities initiated in FY 1992 or for the Department's share for continuing operations.

"Document Control for Division of Life Sciences"

TYPE: ACTION
ORIGINATOR: 02

STATUS I
DOCUMENT NUMBER: 9202025
DIRECTORATE STATUS C

FROM: JACKSON, Richard L.

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 05/28/92

SUBJECT: HE IS WRITING TO PRESIDENT BUSH, VICE PRESIDENT
QUAYLE, AND DR. BROMLEY TO SEEK THEIR ASSISTANCE
WITH HAVING HIS AIDS DRUG TESTED BY A COMPETENT DRUG
COMPANY.

DIRECTORATE
ASSIGNED: LIFE SCIENCES
STAFF
ASSIGNED: D.A. Henderson

ACTION
REQUIRED: AS NECESSARY
STAFF
ACTION: AS NECESSARY

OSTP DUE DATE: SENDER'S DUE DATE:
DATE COMPLETED: 06/17/92
STAFF DUE DATE 06/17/92
DATE COMPLETED/DEPT: 06/05/92

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #: CONTACT PERSON:
REMARKS: Per Dr. Henderson, "No reply".dic
PHONE: EXT:

OSTP RECEIVED: 06/03/92
FILE: P-LIFE SCIENCES

DEPT RECEIVED: 06/04/92

CENTRAL FILES:



"Document Control for Division of Life Sciences"

TYPE: ACTION DOCUMENT NUMBER: 9202025
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS I

FROM: JACKSON, Richard L.

TO: DR. D.A. BROMLEY

No reply

DATE OF
CORRESPONDENCE: 05/28/92

SUBJECT: HE IS WRITING TO PRESIDENT BUSH, VICE PRESIDENT
QUAYLE, AND DR. BROMLEY TO SEEK THEIR ASSISTANCE
WITH HAVING HIS AIDS DRUG TESTED BY A COMPETENT DRUG
COMPANY.

DIRECTORATE STAFF
ASSIGNED: LIFE SCIENCES ASSIGNED: D.A. Henderson

ACTION STAFF
REQUIRED: AS NECESSARY ACTION: AS NECESSARY

SENDER'S DUE DATE:
OSTP DUE DATE: 06/17/92 STAFF DUE DATE 06/17/92
DATE COMPLETED: DATE COMPLETED/DEPT:

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #: CONTACT PERSON:
REMARKS: PHONE: EXT:

OSTP RECEIVED: 06/03/92 DEPT RECEIVED: 06/04/92
FILE: P-LIFE SCIENCES
CENTRAL FILES:

2025
May 28, 1992

President George Bush (or)
Vice President Dan Quayle. (AND Mr. Bromley)
Washington DC.

Dear Mr. President or Mr. Vice President,
I am a Medical Scientist who has recently discovered a very powerful drug for AIDS (see included drug proposal and resume). Please believe me that the design is rational since the US. Armys Walter Reed Medical Center and AMGEN are currently considering manufacturing and testing this drug which is called Trans-Activated Defensin (TAD).

I am writing to you to ask your help since I was fired from a Pharmaceutical company (Baxter Hyland Division) in January of this year, three months after attempting to patent/develop the potential drug. The excuse provided by my previous employer was, believe it or not, "I was not performing the work I was hired to do". Also, despite the fact I was fired for attempting to make a drug for AIDS, I was threatened with blacklisting if I were to give out my idea to anyone else in the World! The apparent reason for termination and the threat was that the company is currently working on a version of this type of drug (I had no knowledge of that fact), and they did not want to manufacture two versions. Unfortunately, I had only provided Baxter with an incomplete design in October of 1991, and while I was unemployed I completed the design which is probably the best in the World at this time.

Specifically, I would like your assistance in getting some competent drug company to make and test this drug. Understandably, the Presidential Office is not an Employment service or Drug company, but as you are very aware, AIDS is a National security and World threat.

Lastly, I feel that it would be appropriate if Baxter Hyland were sued for what they did to me. Currently I cannot afford my own attorney because Baxter has not consistently authorized my unemployment benefits. Therefore, I am attempting to find anyone who will represent me in spite of my current poverty.

I would greatly appreciate your help if you can offer it.

Respectfully,


Richard L. Jackson
PO Box 771
Agoura Hills, Ca. 91376

Withdrawal/Redaction Sheet

(George Bush Library)

Document No. and Type	Subject/Title of Document	Date	Restriction	Class.
01. Proposal	Research proposal and resume [personal information redacted] (10 pp.)	4/92	(b)(4), (b)(6)	

Collection:

Record Group: Bush Presidential Records
Office: Science and Technology Policy, Office of (OSTP)
Series: Bromley, D. Allan, Files
Subseries: General Science Files
WHORM Cat.:
File Location: Life Sciences: General [6 of 7] [1992]

Date Closed:	3/16/2010	OA/ID Number:	62039-002
FOIA/SYS Case #:	2005-0336-F	Appeal Case #:	
Re-review Case #:		Appeal Disposition:	
P-2/P-5 Review Case #:		Disposition Date:	
AR Case #:		MR Case #:	
AR Disposition:		MR Disposition:	
AR Disposition Date:		MR Disposition Date:	

RESTRICTION CODES

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

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 (b)(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
 (b)(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
 (b)(9) Release would disclose geological or geophysical information

7864

April 3, 1992

Mr. Allen Black Bromely
Advisor to the President for Science & Technology
Room 358 17 NW. O.E.O.B.
Washington DC 20250

Enclosed is a copy of a letter I recently sent to President Bush. I do not expect a meaningful reply. The President needs help but he is surrounded by persons who cannot understand my proposals nor that developed Nations are in a hiatus.

This is a New Age. New Age technologies make it possible to increase the efficiency of most resources by 1 to 10 times. No appropriated funds are required.

The application of these two truths could solve or partly solve most of the problems faced by the USA.

Governments, Academia and Foundations are archaic in their thinking about infra-structures needed for this New Age.

Respectfully,

Gwynn Garnett, Chm. F&LS
2435 N. Lincoln Street
Arlington, Va. 22207

June 1, 1992

Dear Mr. President:

You are losing the up-coming election because you lack politically acceptable ideas to deal with the problems faced by the Nation. This is a New Age. Your advisors are giving you Band Aids and patches when you need fundamental thinking. Perot is a sham but he will beat you unless you access thinkers.

I have worked all over the world for fifty years on New Age Ideas you need. It is so simple it pains me to commit it. There are two pre-requisites for lifting the USA out of its back-wardness, the recession, full employment, family life styles that fit, foreign aid as needed, world leadership, without appropriated funds: the 2 pre-requisites are:

1. A Globalized Information Exchange for Food & Life Systems

—2. Procedures to Evaluate the Nutritional and Toxic constituents of foods and feeds, routinely.

Details for both have been worked out for the private sector to serve rural and urban families; both should be profitable within a few months because much of the work needed has been done. The grow-potential is enormous.

The pre-equisities have proven too distant from old ways of doing things to be explained to reachable officials of governments, the media, academia, banks or industries. Therefore the simple concepts must be demonstrated. The logical place for the demonstration is N. Virginia where most everything is in place to bring the demonstration online in 1992 & 1993.

The demonstration will show what can be done with the New Age technologies but on a small and replicatable scale. Garnett/CBS will charge from \$100,000 to \$250,000 for each new Module it brings online in the USA or in other countries. Others are invited to do all or any part of the work needed to bring new Modules online. Approved foreign currencies will be accepted.

After the Information Exchange and the Food Evaluation Service are in business and F&LS has been demonstrated, entrepreneurs should address the following and many more intractable problems as profitable business ventures, almost anywhere in the world, without appropriated funds:

Unemployment
Tele-commuting
Lifestyles
Foreign Aid
Indian Affairs
Health Care/Cost

Housing
Environment
Ghettos
Hunger
Drugs
Health

Water shortage
Alternative Energy
Trade/Balances
Rain Forests
Waste Management
Repatriation of C

I do not expect a meaningful reply to my letter to the President. If you are interested, send two very knowledgeable, very intelligent, computer-wise and imaginative persons to work in my home in Arlington. Va. for three days.

"Document Control"

TYPE: MEETING REQUEST DOCUMENT NUMBER: 9201069
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS

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

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 03/27/92

SUBJECT: HE REQUESTS TO MEET WITH DR. BROMLEY OR OSTP STAFF
TO DISCUSS THE PROBLEMS AFFECTING IMPLANTABLE
MATERIALS.

DIRECTORATE STAFF
ASSIGNED: LIFE SCIENCES ASSIGNED:

ACTION STAFF
REQUIRED: AS NECESSARY ACTION:

SENDER'S DUE DATE:
OSTP DUE DATE: 04/16/92 STAFF DUE DATE
DATE COMPLETED: DATE COMPLETED/DEPT:

COPIES TO: D. Allan Bromley

WHITE HOUSE TRACKING #: CONTACT PERSON:
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OSTP RECEIVED: 03/31/92 DEPT RECEIVED:
FILE: P-LIFE SCIENCES
CENTRAL FILES:

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**Journal of
LONG-TERM EFFECTS
of MEDICAL IMPLANTS**

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92 MAR 31 P 1: 13

Editor-in-Chief: **Stephen D. Bruck, M.D., Ph.D.**
Stephen D. Bruck Associates, Inc.
Biomaterials and Medical Devices Consulting Group
P. O. Box 828
Rockville, MD 20848-0828
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Associate Editors: **Frederick H. Silver, Ph.D.**
University of Medicine and Dentistry of New Jersey

Subrata Saha, Ph.D.
Louisiana State University Medical Center

Publisher: CRC Press, Inc.
2000 Corporate Blvd., N.W.
Boca Raton, FL 33431

Anthony G. Gristina, M.D.
The Musculoskeletal Sciences Research Institute

March 27, 1992

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

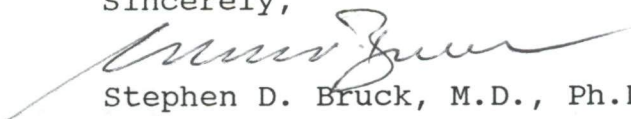
Dear Dr. Bromley:

I am enclosing a letter that I sent to Dr. Bernardine Healy, Director of the National Institutes of Health, dated March 20, 1992 concerning biomaterials.

The key message of my letter is that the problems affecting implantable materials ("biomaterials") are biologic rather than those of materials science and engineering; the field has been overly dominated by engineering approaches; the medical devices industry has not adequately supported basic research in the biologic and clinical sciences, unlike the pharmaceutical industry; and consequently, we should encourage greater industrial funding of research in the biomaterials area before creating new, self-perpetuating enterprises with public funds.

I would welcome an opportunity to discuss the above with you and/or your staff. Please let me know of your availability.

Sincerely,


Stephen D. Bruck, M.D., Ph.D.

Enc.

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Anthony G. Gristina, M.D.
The Musculoskeletal Sciences Research Institute

March 20, 1992

Bernardine Healy, M.D.
Director
National Institutes of Health
Building 1, Room 126
Bethesda, MD 20894

Dear Dr. Healy:

I am writing in reference to the presidential initiative for materials research, especially as it may impact on biomaterials activities within the priorities of the National Institutes of Health.

As you know, the National Heart, Lung, and Blood Institute has been generously supporting, since 1964, research and development of biomaterials, especially for implantable cardiovascular devices and total artificial hearts. This enterprise was initially run, almost exclusively, via contracts. Subsequently, the contractual mechanism was supplemented by grants, both RFAs and others.

While "the jury is still out" on "permanent" mechanical hearts, it is fair to say that the materials (polyurethanes) used therein have been essentially developed for industrial uses (e.g., du Pont). It is also possible to predict from available scientific knowledge base that these materials are not suitable for long-term (years) reliable performance, a circumstance that is unfortunately being simplistically ignored. The situation resembles, in some ways, the demise in 1991 of polyurethane-covered silicone mammary prostheses and failures of some polyurethane-covered cardiac pacemaker leads.

Next, I would like to comment briefly on other materials used in medical implants. Polymethylmethacrylate has been used increasingly since the second World War in IOLs and also as bone cement in orthopaedic prostheses. Hydrogels, based on 2-hydroxyethylmethacrylate, were developed in Czechoslovakia by Wichterle and Lim for soft contact lenses in the 1960s. Among the oldest polymers used in biomedical applications are silicone elastomers, developed by scientists at the Dow Corning Company. I should also mention biodegradable lactides and glycolides used in surgical sutures, developed at the Ethicon Company (Johnson and Johnson), and various polyesters originating from the Du Pont Company, used, among others, in blood conduits. Polyvinyl chloride (PVC) is perhaps the most widely used polymer in disposable medical applications, such as blood bags and transfusion supplies, despite the fact that it contains up to 55% by weight of leachable phthalic esters. Patients on renal dialysis receive as much as 26 mg per session of this leachable component that is known to reach the liver, metabolize there to toxic intermediates, and also is deposited in the fatty tissues. PVC is a very cheap material and has certain desirable properties, such as clarity and processability by conventional thermal methods. This cheap material could, however, be readily displaced by several non-leaching polymers. There exist adequate technology and know-how to do this. It is not being done because of the profit and market domination by a few companies. It is curious that these problems have not received the wide publicity that silicone-gel filled silicone mammary implants have. However, it would be a folly to expend public monies to "develop" alternate materials to replace PVC for biomedical uses because industry could quite easily do so with the prodding of the FDA.

As the above discussion indicates, most materials used today by industry for medical application had their origins in non-biomedical areas that is not necessarily bad. Unfortunately, however, many of these materials have been renamed with appealing tradenames, carrying biologic and medical connotations for marketing purposes, thus giving the impression that they are "new". Many physicians and the public have been poorly informed as the result of this situation. It is similar to the proliferation of numerous over-the-counter, redundant drugs with miniscule differences in their formulations and little, if any, real therapeutic benefits.

So-called "pure" materials can be prepared in the laboratory and studied there for their hemocompatibility, biocompatibility, and other propensities. However, such materials especially polymers, must eventually be formulated with additives so that they may be amenable to industrial production methodologies and configured into devices. Therefore, the "pure" biomaterial studied in vitro no longer resembles the final product. Each device requires its own

criteria for functioning in the physiological environment reliably during its intended performance-life. In other words, there are no universal formulas amenable for all applications, with the exception that the materials should be non-toxic, should not produce immune reactions, and be relatively benign to the biological environment.

Despite the generous financial support to individual investigators and academic centers since 1963 by the NIH, there has been actually very limited progress in the area of biocompatibility of materials. Surface phenomena have been largely "outmined" scientifically and seem to have contributed little to the clinical performance of polymeric materials, other than to clutter the literature with redundant in vitro data of adsorption kinetics of various proteins that, most often than not, have offered few clinically useful benefits. I would like to call your attention to my editorial in volume 1, issue 4, pages 293-294, 1992 of the Journal of Long-Term Effects of Medical Implants, entitled "Surface Phenomena of Biomaterials Revisited". A copy of this issue of the Journal is enclosed with my compliments.

Today, we are not much closer in our understanding the principles involved in biocompatibility, hemocompatibility, and immunologic behavior of implants than we were some 15 years ago, despite the generous grant support by the NIH. Synthetic efforts for improving say polyurethanes and polyesters have, at best, yielded marginal results in vitro that generally did not hold up in vivo. Perhaps, the most significant achievement was that of Vincent L. Gott, M.D. and colleagues of The Johns Hopkins University School of Medicine, with ionically-bound heparin to graphite surfaces in the 1961 for short-term in vivo uses. This was done without NIH grant monies. Since then there have appeared a multitude of papers more or less imitating this surface modification with other agents, well-subsidized by NIH grants.

Things have not been different elsewhere, including Japan, where public research support is far more limited than in the U.S. So, there should be no paranoic fear of competition that currently prevails in the automobile industry.

During the past 30 years, the field of biomaterials research and development has been overly dominated by engineering approaches. Directed contract efforts, RFAs, and other so-called "coordinated" efforts did not significantly advance this area, other than effectively supporting faculty salaries, and graduate as well as post-doctoral students. We still lack adequate basic knowledge that are not amenable to mammoth centralized efforts. As may be seen by the so-called War on Cancer, even investigator-initiated efforts could not produce, in the time-frame originally envisioned, a magic cure of cancer. It is not unlikely that future cancer "breakthroughs" may come from sources in other areas.

Since 1943 renal dialysis has become universally accepted. The machines have been referred often as "artificial organs". They are not. Today, almost 50 years later, we still do not have an implantable, "self-propelled", artificial kidney. Instead, we have countless, highly profitable dialysis centers, and millions of patients needing dialysis or renal transplants world-wide. There have been incremental improvements in dialysis membranes but the technology has not changed much. There seems to be a comfortable stagnation with the status quo. At the same time, thousands endure suffering, loss of income, and many have become paupers.

Certain highly special applications of biomaterials need entirely new approaches that are not typical of what is currently known as "materials science and engineering". They need the utilization of some of the tools and concepts of molecular biology and far less of engineering. In some ways, the problems do not even involve "materials science".

The great majority of annual kilogram production and consumption of materials used in medical applications involves disposables, storage containers, and packaging. Not implants. Materials used in disposables, storage containers, and packaging are not biomaterials. In the area of implants, the economic profits for industry are in the devices rather than in their component materials. For example, a cardiac pacemaker lead contains a very small quantity of silicone or polyurethane, costing a few cents. Yet, the pacemaker leads sell for hundreds of dollars. The same applies to other implantable devices. Thus, there is much room for industrial effort to better select and utilize existing materials and to support in-house research and development and in academic centers. Fruitful collaboration already exists between Washington University (St. Louis, MO) and the Monsanto Company.

While an informed public is desirable, the biomaterials field does not need slick educational advertising and promises aimed at the gullable that sooner or later are forgotten or, when failures become apparent, are often quietly redirected to generate justifications for further public monies. The American public is being constantly bombarded by occasional spectacles of health-related "firsts" that are inducing fears and paranoia but which have all too often not resulted in improved health benefits for substantial segments of our population or even to anyone.

The fantastic health-care costs and associated social inequities in the United States of America have constantly grown in direct proportion to self-serving, induced stresses and proliferation of redundant, often marginal gadgetry. The FDA could easily weed out many of these that would reduce hospital costs. As I understood your various statements in the public press, the NIH's over nine billion dollars per year budget will increasingly obligate it to

consider issues that are not viewed by many to be traditionally within the boundaries of academic research matters.

The medical implant field needs much greater expenditures by industry for basic and applied research, especially in the area of biologic sciences, than what is currently the case. It needs better utilization by industry of existing scientific knowledge.

Many premature failures of implantable devices can be traced to gross ignorance of the physiologic environment and pressures for early commercialization with generation of fast profit.

Many problems involving biomaterials (and I especially limit this to components of medical implants that are in contact with the living system) have biologic causes. Unfortunately, as I noted above, these have often been deemphasized. Some of the best brains in the U.S. have "fled" the biomaterials field that has been long-dominated by interlocking, vocal groups intended to maintain the status quo. It is unlikely that new, taxpayer supported and centralized efforts would remedy the above exigencies under the disguised label of public health benefits. However, the NIH could influence the future by judicious reexamination of its grant mechanism.

The majority of the pharmaceutical industry does a fairly good job in performing and supporting fundamental research. Not so the majority of the medical device industry. It will have to do better. Let us seriously encourage that goal before we create new, self-perpetuating enterprises with public funds.

My discussions with distinguished members of our Editorial Board and the Associate Editors indicate that they share the views expressed in this letter. I would welcome the opportunity for an exchange of ideas with you and members of your policy staff. I feel that you may find such discussions helpful in your current efforts in setting the priorities for the National Institutes of Health. Please let me know of your availability.

Sincerely,



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

Enc.

JOURNAL OF LONG-TERM EFFECTS OF MEDICAL IMPLANTS

Volume 1, Issue 4, 1992

EDITORIAL

Surface Phenomena of Biomaterials Revisited

After more than 25 years of research, the availability of increasingly sophisticated instrumentation, and generous financial support by federal government agencies, *in vivo* surface phenomena in the case of synthetic polymeric biomaterials remain enigmatic. Inasmuch as most such materials have been developed for uses other than biomedical applications, they contain various, often unspecified proprietary additives, inhibitors, traces of catalysts, and other agents, that can migrate to the surface in the physiological environment. Hence, what was once in the bulk will appear at the surface, giving rise to a continuously changing interface with the physiologic milieu. More often than not, experiments conducted *in vitro* using various test solutions and static conditions led to conclusions and predictions that do not reflect the ultimate performance of materials *in vivo*. While polymeric medical implants will adsorb (as well as absorb) various biologic components when in contact with the physiologic milieu, the initial adsorption process is not only influenced by the nature of the materials' surface, but importantly also by the "impurities" that have migrated to the surface from the bulk. In most cases, the distribution of these vary, to some extent, from batch-to-batch (as the result of even small variations in processing conditions), thus further complicating the situation.

It should be noted that prior to the arrival of biologic components (including plasma proteins in the case of blood contact) at the interface, small ionic species will be adsorbed that, in turn, influence the surface phenomena. While the adsorption of various plasma proteins on surfaces have been more than amply demonstrated *in vitro*, its long-term clinical relevancy in the dynamic physiologic environment remains largely obscure. This seems to be related to the lack of sufficient emphasis on biological events in favor of physico-chemical and engineering characteristics of materials. The fact is that bulk and surface properties, as well as dynamic biologic events, form an integral, dynamic, interlocking unit that must be considered in predicting the long-term effects of implants, rather than focusing exclusively on one or the other.

Closely related to the enigma of *in vivo* surface phenomena is the problem of biocompatibility. This has been often and simplistically related, almost exclu-

sively, to surface properties of materials, and/or to the absence of toxic responses. Biocompatibility, however, implies benign behavior of a given material towards the dynamic, physiologic environment **and** simultaneous benign responses of the dynamic physiologic environment towards the implanted material during its intended period of performance. This reciprocal relationship seems to be the *sine qua non* for long-term biocompatibility.

Confusing and simplistic data bases are also increasingly cited in the literature as "evidence" for enzyme-catalyzed hydrolyses of polymeric biomaterials, presumably starting at surfaces. In fact, to date, there are only three documented cases where synthetic polymeric materials undergo enzyme-catalyzed hydrolyses *in vitro* and, apparently, also *in vivo*, excluding polymers that contain peptidic-, glycosidic-, or phosphatidic bonds. Most attempted extrapolations from *in vitro* to *in vivo* conditions are unwarranted because they are not supported by sufficient scientific criteria. Thus, the factors affecting the long-term biodegradation of materials and implants remain largely elusive.

The above problems call for entirely new approaches, including the utilization of some of the tools and concepts of molecular biological chemistry.

Stephen D. Bruck, Ph.D.

Editor-in-Chief

[97] From: Raub William F. 4/20/92 3:16PM (237 bytes: 2 ln)

To: Coleman Donna I.

Subject: Letter to Bruck

----- Message Contents -----

The text is on H as BRUCK. The related stuff is in my
outbox. Please print. Thanks.

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

April 22, 1992

Dear Dr. Bruck:

This is in response to your letter of March 27 to Dr. D. Allan Bromley regarding biomaterials.

I share your view that biomaterials present many formidable research challenges, especially with respect to understanding the biological events at the interface between living tissues and implant material. As the concepts and techniques of molecular and cell biology continue to mature, many more of these topics should become accessible to an experimental approach than heretofore. The prospects seem bright, therefore, for a well-balanced effort across the spectrum from basic science to selected engineering efforts. This indeed is one of the objectives of the Advanced Materials and Processing Initiative of the Committee on Industry and Technology of the Federal Coordinating Council on Science, Engineering, and Technology.

The National Institutes of Health is a participant in the Initiative mentioned above and as such provides an indispensable life-sciences perspective on the research opportunities emerging in the wake of advances in materials-science and engineering. Moreover, Dr. Healy and her staff now are addressing a host of generic questions related to strategic planning and priority setting - matters that obviously have a bearing on biomaterials research and development as well as many other areas. Your letter to NIH thus is both properly placed and timely; and I feel certain that it will receive thoughtful attention.

Sincerely yours,



William F. Raub, Ph.D.
Special Assistant for Health Affairs

Stephen D. Bruck, M.D., Ph.D.
Stephen D. Bruck Associates, Incorporated
Biomaterials and Medical Devices
Consulting Group
P.O. Box 828
Rockville, MD 20848-0828

bcc: D. Allan Bromley

"Document Control for Division of Life Sciences"

TYPE: MEETING REQUEST DOCUMENT NUMBER: 9201069
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

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

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 03/27/92

SUBJECT: HE REQUESTS TO MEET WITH DR. BROMLEY OR OSTP STAFF
TO DISCUSS THE PROBLEMS AFFECTING IMPLANTABLE
MATERIALS.

DIRECTORATE STAFF
ASSIGNED: LIFE SCIENCES ASSIGNED: William Raub

ACTION STAFF
REQUIRED: AS NECESSARY ACTION: Necessary Action

SENDER'S DUE DATE:
OSTP DUE DATE: 04/16/92 STAFF DUE DATE 04/16/92
DATE COMPLETED: DATE COMPLETED/DEPT: 04/22/92

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DEPT RECEIVED: 04/03/92 .



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

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Rockville, MD 20848-0828

bcc: D. Allan Bromley

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FROM: DEB, Sumitra: UNIVERSITY OF TEXAS

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 03/23/92

SUBJECT: HE IS REQUESTING ASSISTANCE WITH HIS PROPOSAL TO
NIH.

DIRECTORATE STAFF
ASSIGNED: LIFE SCIENCES ASSIGNED:

ACTION STAFF
REQUIRED: AS APPROPRIATE ACTION:

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necessary*

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02. Letter w/ attachments	To: Allan Bromley From: Sumitra Deb Re: Proposal to NIH [NIH responses attached] (21 pp.)	3/23/92	(b)(4), (b)(6)	

Collection:

Record Group: Bush Presidential Records
Office: Science and Technology Policy, Office of (OSTP)
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Subseries: General Science Files
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Re-review Case #:		Appeal Disposition:	
P-2/P-5 Review Case #:		Disposition Date:	
AR Case #:		MR Case #:	
AR Disposition:		MR Disposition:	
AR Disposition Date:		MR Disposition Date:	

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