- P. Cohen et al., in Metabolic Interconversions of Enzymes 1980, H. Holzer, Ed. (Springer-Verlag, Heidelberg, 1981), p. 28.
 B. A. Hemmings, T. J. Resink, P. Cohen, FEBS Lett. 150, 319 (1982); T. J. Resink, B. A. Hem-mings, H. Y. Lim Tung, P. Cohen, Eur. J. Biochem., in press.
 J. Goris, G. Defreyn, W. Merlevede, FEBS Lett. 99, 279 (1979); J. Goris, F. Dopere, J. R. Vandenheede, W. Merlevede, *ibid*. 117, 117 (1980); S. D. Yang, J. R. Vandenheede, J. Goris, W. Merlevede, J. Biol. Chem. 255, 11759 (1980).
- (1980); S. D. Yang, J. R. Vandenheede, J. Goris,
 W. Merlevede, J. Biol. Chem. 255, 11759 (1980).
 22. D. L. Brautigan, C. Picton, E. H. Fischer, Biochemistry 19, 5784 (1980); D. L. Brautigan,
 L. M. Ballou, E. H. Fischer, *ibid.* 21, 1977 (1982); J. R. Vandenheede, S. D. Yang, W. Merlevede, J. Biol. Chem. 256, 5894 (1981); R. L. Mellgren, J. H. Aylward, S. D. Killilea, E. Y. C. Lee, *ibid.* 254, 648 (1979).
 23. M. D. Pato and R. S. Adelstein, J. Biol. Chem. 255 (535 (1980))
- M. D. Pato and K. S. Adeistein, J. Biol. Chem. 255, 6535 (1980). S. Tamura and S. Tsuiki, *Eur. J. Biochem*, 111, 217 (1980); D. Crouch and B. Safer, *J. Biol. Chem*, 255, 7918 (1980); S. Tamura, H. Kikuchi, W. Witter, J. Misson, S. Taulti, *Eur. J. Bio*. 24 Chem. 253, 1916 (1960), S. Tahuha, H. Rikolni, K. Kikuchi, A. Hiraga, S. Tsuiki, Eur, J. Bio-chem. 104, 347 (1980); D. K. Werth, J. R. Haeberle, D. R. Hathaway, J. Biol. Chem. 257, 7306 (1982).

- 27. J. H. Wang and R. Desai, J. Biol. Chem. 252, 4175 (1977); R. K. Sharma, R. Desai, D. M. Waisman, J. H. Wang, *ibid*. **254**, 4276 (1979).
- C. B. Klee, T. H. Crouch, M. H. Krinks, *Proc. Natl. Acad. Sci. U.S.A.* 76, 6270 (1979).
 R. W. Wallace, E. A. Tallant, W. Y. Cheung, *Biochemistry* 19, 1831 (1980).

- P. Cohen, C. B. Klee, C. Picton, S. Shenolikar, Ann. N.Y. Acad. Sci. 356, 151 (1980); P. Cohen, Eur. J Biochem. 111, 563 (1980); C. Picton, C. B. Klee, P. Cohen, Cell Calcium 2, 281 (1981).
 J. F. Binstock and H. C. Li, Biochem. Biophys. Res. Commun. 87, 1226 (1979); K. Kikuchi, S. Tomuro, A. Hieron, S. Touilti, ikid. 25, 20 Tamura, A. Hiraga, S. Tsuiki, *ibid*. **75**, 29 (1978); C. W. MacKenzie, G. J. Bulbulian, J. S. (19/8); C. W. MacKenzie, G. J. Buboman, J. S. Bishop, *Biochim. Biophys. Acta* **614**, 413 (1980).
 A. Hiraga, K. Kikuchi, S. Tamura, S. Tsuiki, *Eur. J. Biochem.* **119**, 503 (1981).
 G. A. Nimmo and P. Cohen, *ibid.* **87**, 341 (1978);
 A. A. Kimmo and P. Cohen, *ibid.* **87**, 341 (1978); 32.
- A. Aitken, T. Bilham, P. Cohen, *ibid*. 126, 235 (1982) J. G. Foulkes and P. Cohen, *ibid.* 105, 195
- 34. J. G. Foulkes and P. Cohen, *Ibid.* 105, 195
 (1980); S. D. Yang, J. R. Vandenheede, W. Merlevede, *FEBS Lett.* 132, 293 (1981).
 B. A. Hemmings, D. Yellowlees, J. C. Kernohan, P. Cohen, *Eur. J. Biochem.* 119, 443 (1981).
 J. G. Foulkes and P. Cohen, *ibid.* 97, 251 (1979).
 J. G. Foulkes, L. S. Jefferson, P. Cohen, *FEBS Lett.* 112, 214 (1980). J. G. Foulker, P. Cohen, *FEBS Lett.* 112, 214 (1980).
- *Lett.* **112**, 21 (1980); J. G. Foulkes, P. Cohen, S. J. Strada, W. V. Everson, L. S. Jefferson, *J.*
- J. Strada, W. V. Everson, L. S. Jenerson, J. Biol. Chem. 257, 12493 (1982). P. J. Parker, N. Embi, F. B. Caudwell, P. Cohen, Eur. J. Biochem. 124, 47 (1982). T. S. Ingebritsen and D. M. Gibson, in Molecu-38. 39.
- lar Aspects of Cellular Regulation, P. Cohen, Ed. (Elsevier/North-Holland, Amsterdam, 1980), Vol. 1, p. 63; T. S. Ingebritsen, in Monographs in Enzyme Biology, J. R. Sabine, Ed. (CRC Press, Boca Raton, Fla.), vol. 1, in press. Z. Damuni, F. B. Caudwell, P. Cohen, Eur. J. Biochem. 129, 57 (1982).
- 40. Ž 41. D. E. Koshland, Annu. Rev. Biochem. 50, 765
- (1981)42.
- P. J. Parker, F. B. Caudwell, P. Cohen, *Eur. J. Biochem.* 130, 227 (1983).
- S. D. Yang, J. R. Vandenheede, W. Merlevede, J. Biol. Chem. 256, 10231 (1981); J. R. Vanden-heede, J. Goris, S. D. Yang, T. Camps, W. Merlevede, FEBS Lett. 127, 1 (1981).

- P. S. Guy, P. Cohen, D. G. Hardie, Eur. J. Biochem. 114, 399 (1981); M. W. Pierce, J. L. Palmer, H. T. Keutmann, J. Avruch, J. Biol. Chem. 256, 8867 (1981); N. S. Raganthan, T. C. Linn, P. A. Srere, ibid. 257, 698 (1982); D. G. Hardie and P. S. Guy, Eur. J. Biochem. 110, 167 (1980); J. P. Tipper and L. A. Witters, Biochim. Biophys. Acta 715, 162 (1982); L. Engstrom, in Molecular Aspects of Cellular Regulation, P. Cohen, Ed. (Elsevier/North-Holland, Amster-dam, 1980), vol. 1, p. 11.
 R. Jagus, D. Crouch, A. Konieczny, B. Safer, Curr. Top. Cell. Regul. 21, 36 (1982).
 V. Ernst, D. H. Levin, J. G. Foulkes, I. M. London, Proc. Natl. Acad. Sci. U.S.A. 79, 7092 (1982); J. G. Foulkes, V. Ernst, D. H. Levin, J. Biol. Chem. 258, 1439 (1983).
 R. S. Adelstein and E. Eisenberg, Annu. Rev. Biochem. 49, 921 (1980).
 B. K. Kreuger, J. Forn, P. Greengard, J. Biol. Chem. 252 (24) (1972).

- B. K. Kreuger, J. Forn, P. Greengard, J. Biol. Chem. 252, 2764 (1977).
- Chem. 252, 2764 (1977).
 D. Huchon, R. Ozon, J. G. Demaille, Nature (London) 294, 358 (1981); J. G. Foulkes and J. L. Maller, FEBS Lett. 150, 155 (1982).
 L. J. Reed, F. A. Pettit, D. H. Bleile, T. L. Wu. 1997.
- L. J. Reed, F. A. Pettit, D. H. Bleile, I. L. Wu, in *Metabolic Interconversions of Enzymes 1980*, H. Holzer, Ed. (Springer-Verlag, Heidelberg, 1981), p. 124; M. L. Pratt, J. F. Maher, T. E. Roche, *Eur. J. Biochem*, **125**, 349 (1982).

- Roche, Eur. J. Biochem. 125, 349 (1982).
 51. T. Hunter, Trends Biochem. Sci. 7, 246 (1982).
 52. J. G. Foulkes, E. Erikson, R. L. Erikson, J. Biol. Chem. 258, 431 (1983).
 53. J. R. Woodgett, N. K. Tonks, P. Cohen, FEBS Lett. 148, 5 (1982).
 54. J. Goris, T. Camps, G. Defreyn, W. Merlevede, *ibid.* 134, 189 (1981); G. Defreyn, J. Goris, W. Merlevede, *ibid.* 19, 125 (1977).
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again-off-again funding will dissuade many scientists from research pursuits. To maintain our capacity in biomedical research, which has become one of the country's greatest resources, and to

additional \$300 million (the total NIH

appropriation was about \$3.6 billion) to fully fund, for 1 year, 50 percent of the

approved competing grant applications (2). There could be no better investment

Until this fiscal goal can be attained,

some measures are required to avoid

serious damage to our hopes of progress.

A letter to Science (3) expressed the

concern of the Association for Medical

School Pharmacology about the future of

our biomedical research capacity. Under

the present procedure for awarding the

available funds, many excellent research

projects are being terminated or cannot

in the health of our nation.

Funding More NIH Research Grants

Proposals of a multidisciplinary group of biomedical scientists

H. George Mandel

Biomedical scientists are acutely aware of the growing inadequacy of financial support for research. Proposals to the National Institutes of Health (NIH) that are highly rated by peer review and that a few years ago would have been funded are now without support. In constant dollars, NIH appropriations for competing research projects (1)have actually gone down since 1979. The number of eligible applications submitted and recommended for payment by study sections has been growing steadily, but the number of awards has remained unchanged or has declined (Fig. 1).

The country's capacity for biomedical research, which has been built during many years of encouragement and support from the federal government, and which has been dramatically effective in improving our understanding of the basis of many human diseases and the design of rational treatment, is rapidly deteriorating. At the present time we lack the program stability needed to continue to attract and retain capable young scientists in biomedical research, and on-

provide the stability and diversity essential to it, federal appropriations for biomedical research must be increased. For fiscal 1982 it would have required an

Members of the group are Irwin Fridovich, president of the American Society of Biological Biochemists (ASBC): Lowell M. Greenbaum, secretary of the Association for Medical School Pharmacology (AMSP); Harold F. Hardman, president of the American Society for Pharmacology and Experimental Therapeutics (ASPET); H. George Mandel, chairman of a subcommittee of ASPET on NIH funding procedures and policies; Alan H. Mehler, chairman of ASBC's ad hoc Committee on Research Support; Gerald C. Mueller, president of the American Association for Cancer Research; Walter C. Randall, president of the American Physiological Society; Dante G. Scarpelli, president of the American Association of Pathologists; Frank G. Standaert, president of AMSP; William J. Whelan, president of the Association of Medical School Departments of Biochemistry; and Julius S. Youngner, president of the Association of Medical School Microbiology Chairmen. The opinions expressed do not necessarily reflect those of the membership of these organizations. John F. Sherman, vice-president of the Association of American Medical Colleges and formerly deputy director of NIH, attended the preliminary meeting as a resource person. Address requests for reprints to H. George Mandel, Department of Pharmacology, George Washington University Medical Center, Washington, D.C. 20037.

be initiated. The selection process that worked well when appropriations were adequate to permit most meritorious projects to be funded is no longer suitable, because the budgeting situation has changed so drastically. In the letter a number of temporary devices were proposed to permit the support of a larger number of scientific programs and investigators, with the average award somewhat reduced, until appropriations become adequate for full utilization of our nation's research resources.

That letter attracted considerable attention, and many members of the scientific community agreed on the urgency of the problem and a need for immediate action. A similar letter from the Association of Medical School Microbiology Chairmen (4), endorsement by the Association of Medical School Departments of Biochemistry, and a resolution from the Board of Directors of the American Association for Cancer Research prompted meetings of elected officers of several biomedical associations on 9 and 10 November 1982 in Washington, D.C.

The group agreed on the general principle that measures should be implemented at once, on a temporary basis, to permit some redistribution of available research funds in order to maintain a maximum diversity of research of high quality, and to provide continuity for research groups that would otherwise have to be disbanded. The participants recognize that the mechanisms proposed for stretching research dollars are far from simple, and that not every scientist would be enthusiastic about a redistribution of existing funds at a time of such severe curtailment. However, many investigators have expressed a willingness to forego a fraction of their individual research support (coupled with a corresponding limitation in research objectives) if such a sacrifice will make possible a greater diversity of biomedical research carried out by a larger segment of the scientific community. It must be recognized that reduction in the size of a grant in no way implies that these grants have been funded excessively in the past; a corresponding curtailment of the expected scientific efforts would have to accompany any decrease in the funds awarded. The National Science Foundation has had considerable experience with partial funding of grant applications, and is finding it workable. All funded research must be of high quality, and the extent of any budget reduction must be monitored by NIH to ensure viability of the remaining project.

In general, the views expressed in the AMSP communication (3) were reaf-

firmed. The group believes that the top 50 percent of applications approved by peer review should be funded, even if necessarily less than fully. A series of specific means to that end were discussed during a subsequent meeting of the entire group with James B. Wyngaarden, director of NIH.

such small differences in scores result from chance rather than merit.

Table 1, based on data for 1982 (2), illustrates the application of a slidingscale model to each of the institutes. The mean award rate in effect during the already lean years 1977 to 1981 has been used as the guide. For several institutes

Summary. Because of the prospect of a serious decline in the nation's biomedical research capacity owing to diminished federal appropriations, temporary measures should be initiated promptly by the National Institutes of Health to preserve the stability of resources and diversity of research required for future productivity. It is recommended that the available funds be distributed in such a way as to permit some support for 50 percent of competing grant applications approved by the National Institutes of Health study sections. Measures proposed for consideration are a sliding scale for funding, a greater across-the-board reduction, a limit on support for an individual laboratory, and a review of indirect costs.

1) A sliding-scale approach, based on the present peer review system and priority score concept, appears to offer a workable and effective procedure, especially if used in conjunction with additional means of redistributing funds. Special consideration obviously is required when the budget for a project consists mainly of costly components that cannot be trimmed or partly supported by some other source. Clearly, it is necessary to insure that sufficient funds remain available for the investigator to achieve reasonable research goals.

Scientists are aware that for most projects the only present alternative to the sliding scale is the absolute cut-off. Thus, large numbers of excellent scientific proposals to which peer review groups have assigned priority scores very close to those of projects being fully funded receive no funds at all. Indeed, the maximum budget reductions in the model appear quite steep, but such cuts affect only a limited number of grants, which otherwise would remain totally unfunded. Scientists who choose to accept these reduced awards would thereby be given an opportunity to continue to contribute to knowledge, and the highly meritorious priority rating received from peer review would justify the expenditure of federal funds. Moreover, the most serious curtailments can be lessened if alternative mechanisms are applied in addition to some sliding-scale option, as for example by spreading the reduction over a larger number of awards, or eliminating certain expenditures. In the particular model provided as an example, the number of awards for competing projects would increase by 924 or 1616, depending on whether the lower or higher award rate bracketing

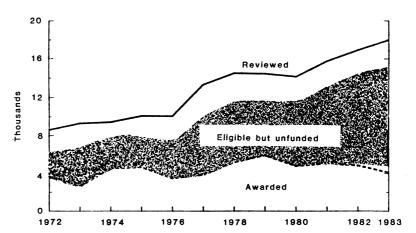


Fig. 1. Number of competing research-project applications to NIH reviewed, eligible, and granted, fiscal years 1972 to 1983. The dashed line for 1982 and 1983 represents estimates based on the budget. Subsequently it became possible to fund 244 additional grants for 1982, for a total of 5027. The larger estimate for 1983 is based on the recently passed congressional continuing resolution which superseded the presidential budget for 1983; it is expected to permit the funding of about 4900 awards. [Data supplied by Extramural Trends, Statistics, and Analysis Branch, Division of Research Grants, National Institutes of Health]

the 5-year mean rate is selected. It should be noted that, in either case, only applications with very desirable priority scores (usually better than 220) are being proposed for funding.

2) An across-the-board reduction in the size of new grants, and renegotiation of all existing grants at the time of renewal, could be effective if applied uniformly. As with the sliding scale, it is assumed that reductions of 20 to 40 percent offer a feasible means of supporting a greater diversity of research. In the past year, small across-the-board cuts have been made by some of the institutes, but greater reductions than those currently in effect will be required in order to produce the desired number of research grants. Again, other options could be combined with this one.

An alternative to across-the-board reductions would be a progressive reduction, very large grants being reduced by a somewhat greater percentage than

Table 1. Number of competing research-project applications budgeted by the NIH institutes for fiscal year 1982 and number that could have been funded from identical total budgets with the operation of a sliding scale. The italicized figures are the preliminary award rates for fiscal 1982 (subject to later adjustments). The award rates selected as examples bracket the mean rate of fiscal years 1977 to 1981. In this particular sliding-scale model each of the graded budgetary reduction steps was set to include one-tenth of the total number of grants that would be funded given the specified award rate, ranked by priority score. No funding cut was applied to grants in the top decile of priority scores, and the maximum reduction affected only the lowest fundable decile. For example, at the National Institute of Allergy and Infectious Diseases, with a 35 percent award rate the 50 grants in the top decile would be paid in full and grants ranked in positions 451 to 50 would be reduced by 48.4 percent. [Data supplied by the Statistics and Analysis Branch, Division of Research Grants, National Institutes of Health]

Institute*	Award rates (% of applications funded)		Reduction in size of grants (%)		Number of grants		Limiting
	Mean, 1977– 1981	1982†	Mean	Maxi- mum	Total	In- crease	priority score‡
Aging	39.5	<i>31.2</i> 35 40	11.5 23.4	21.6 43.1	149 167 191	18 42	204 212 222
Allergy	37.2	26.3 35 40	24.8 33.2	48.4 64.0	377 501 572	124 195	162 178 189
Arthritis	44.1	30.8 40 45	25.7 32.6	49.7 63.5	610 793 892	183 282	181 202 214
Cancer	40.0	29.7 35 40	27.4 37.1	53.4 70.7	740 873 998	133 258	186 198 210
Dental	42.3	<i>39.1</i> 40 45	4.4 14.3	8.1 26.7	107 110 123	3	201 203 208
Environmental	44.8	34.8 40 45	22.0 34.4	39.1 59.8	94 108 122	14 28	227 239 255
Eye	57.9	45.2 50	17.4	33.1	252 279	27	201 208
General	47.2	37.6 45 50	21.5 28.0	41.9 54.3	828 990 1101	162 273	177 190 201
Child	39.8	32.7 35 40	8.7 19.0	16.6 36.6	409 438 500	29 91	188 193 201
Heart	44.4	35.8 40 45	14.3 21.8	25.7 40.2	721 805 906	84 185	195 207 222
Neurology	47.1	34.7 45 50	26.4 33.4	47.7 60.6	496 643 715	147 219	182 207 222
Total	Lower target rate Higher target rate					924 1616	

*More complete identification: Institute on Aging; Institute of Allergy and Infectious Diseases; Institute of Arthritis, Metabolism, and Digestive Diseases; Cancer Institute; Institute of Dental Research; Institute of Environmental Health Sciences; Eye Institute; Institute of General Medical Sciences; Institute of Child Health and Human Development; Heart, Lung, and Blood Institute; Institute of Neurological and Communicative Disorders and Stroke. †Subsequently 244 additional awards (total for all institutes) were made ‡Estimates based on the assumption that funding proceeded strictly in order of priority ranking.

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smaller grants, in the expectation that laboratories with the heaviest support would be able to withstand a somewhat greater budget curtailment.

3) A limit on the total financial support for an individual laboratory would be another means of spreading the distribution of available dollars. This requires analysis of the total governmental and other funds available to and needed by a laboratory, and implies understanding the fiscal structure of the laboratory unit. Special scrutiny is needed before awarding multiple grants to a principal investigator. Such a funding limitation would have to be handled with great care so as not to compromise excellent laboratory programs that function best with large sums going to one principal investigator.

4) An amplification factor can frequently be demonstrated when research teams share major research resources with great efficiency. However, large programs funded by contracts and various umbrella instruments should be evaluated specifically to insure that the quality and quantity of research achieved match the productivity of smaller projects initiated by individual investigators and reviewed with close scrutiny by study sections. A relatively small percentage reduction in the funds for large contracts may permit the funding of several additional grants.

5) The ever-increasing indirect costs of research are further restricting the funds that remain for paying direct costs. Considerable economies can be effected by elimination of unnecessary duplication of accounting and reporting procedures. Further examination of this question should be undertaken.

The participants in these preliminary discussions have agreed to pursue these questions with colleagues and to continue as a group to seek the necessary reforms. They urge other biomedical organizations to join in these efforts. Scientists should express themselves directly through their professional organizations to their colleagues, the National Institutes of Health, and their representatives in Congress. The development and implementation of a long-range national biomedical science policy are essential at this time.

References and Notes

- 1. The term "competing applications" (or projects) refers to new proposals or renewal re-quests, in contrast to continuing projects for which a previous funding commitment has been
- Calculated from data supplied by the Statistics and Analysis Branch, Division of Research Grants, National Institutes of Health.
 E. S. Vesell and H. G. Mandel, Science 215, 1026 (1982).
- 4. J. S. Youngner and K. I. Berns, ibid. 216, 798 (1982).