NIH Moves to Debar Cholesterol Researcher

Report on anticholesterol therapy for children found riddled with errors and "misrepresentations"

A COMMITTEE at the National Institutes of Health (NIH) has recommended that Charles J. Glueck, a prominent cholesterol researcher who has been at the University of Cincinnati for 18 years, be debarred from federal funding for 2 years.

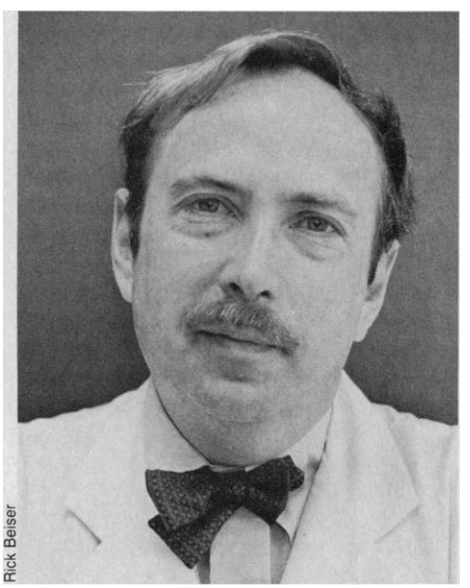
The recommendation was made following an investigation by the university, which alleged "serious scientific misconduct" on the part of Glueck in connection with a paper published in the August 1986 issue of *Pediatrics*.* Glueck, 48, headed the university's General Clinical Research Center and its Lipid Research Center, both of which receive NIH funding. He resigned on 9 February and is now employed by the Jewish Hospital of Cincinnati.

The charges stem from what are regarded as errors and misrepresentations in the report of a study that could be of considerable clinical significance because it bears on the current debate on the safety and efficacy of cholesterol-lowering therapy for children who are at risk for developing heart disease.

The paper reports the results of two therapies—a low-fat, low-cholesterol diet, and diet combined with cholesterol-lowering drugs (resin)—on 73 children with extremely high hereditary cholesterol levels. Children of various ages were followed for roughly 5 years. The researchers concluded that both regimens were effective in lowering plasma cholesterol and that neither therapy had any adverse effects on the subjects' physical development or behavior.

An internal university committee, headed by H. Bruce Bosmann, vice dean for academic affairs, has concluded that the study was not a prospective one, as billed, and that because of "arbitrary" data selection as well as internal inconsistencies and inaccuracies, "no meaningful interpretation of the results published in the *Pediatrics* paper can be made." According to the NIH committee that reviewed the university's findings, headed by George J. Galasso of the Office of Extramural Research, the manner in which the study was conducted and reported is "unacceptable by any scientific standard known to the NIH."

Glueck, in a lengthy rebuttal, has acknowledged that the paper is flawed, but said the errors were "random" in nature and that a subsequent, more thorough analysis of the data did not alter the conclusions. He told *Science* that he and his coauthors strongly believe that the important findings in the paper—on height, weight, and cholesterol levels—are valid.



Rick Beiser

Charles J. Glueck. *Says he was overworked and his errors unintentional.*

Problems with the study were first brought to the attention of NIH by two unnamed individuals at the university in June 1986, before the offending paper was published. The university inquiry was performed in July, and the university wrote the editor to disassociate itself from the article shortly after it appeared in August. Jerold Lucey, the editor of *Pediatrics*, says he is annoyed at NIH for not telling him of the problem before the paper was published so he could have decided whether to delay publication. He says the flaws were not of the type that could have been detected in the peer-review process.

With regard to the first allegation, that the study was not really prospective, the university committee's investigation established that some of the data had been longitudinally collected from studies conducted by Glueck between 1970 and 1977. But, said the committee, the children treated with diet alone "were never included in any protocol and could not be documented as part of any prospective study." It also said that no prospective protocols were provided for follow-up occurring after 1978 (the period covered by the study extended to 1984). "A prospective study does not look backwards to find subjects and criteria," noted the committee.

What's more, the committee found that the control group—39 normal children selected from a private pediatric practice—was selected "at the time of manuscript preparation." So, even though data on them were gathered longitudinally, this was not done according to any protocol related to the study.

The NIH committee was not as upset over the use of the term "prospective," saying that use of the term "was not a clear misrepresentation, given the diversity of opinion in the scientific community on the precise meaning of the term." However, it agreed that the term "implied a degree of rigor in the study design that is not supported by fact."

Overall, the NIH found the Cincinnati committee's conclusions "well grounded." The other primary allegations made are that data in the study are internally inconsistent, and patient charts did not contain data substantiating the findings cited in the paper.

"Particularly egregious," in the opinion of the NIH committee, was the absence of documentation for what Glueck calls "qualitative" data bearing on the subjects' sexual maturation, school performance, and behavioral problems. This information, according to the university committee, was collected spottily and not according to any protocol—"qualitative biobehavioral data were represented as factual whereas raw data barely existed."

The university committee identified a welter of other problems, all of which appear to add up to a sloppy job. These include "major inconsistencies" between original patient charts and tables published in the paper; confusion over "start" and "stop" dates for the therapies; inclusion of data on patients over 18 after their physical growth is presumably complete; and misassignment of some patients from the "diet plus resin" group to the "diet only" group.

*"Safety and efficacy of long-term diet and diet plus bile acid-binding resin cholesterol-lowering therapy in 73 children heterozygous for familial hypercholesterolemia," by Charles J. Glueck, Margot J. Mellies, Mark Dine, Tammy Perry, and Peter Laskarzewski, *Pediatrics* (the journal of the American Academy of Pediatrics), vol. 78, pp. 338–348, 2 August 1986.

Subjects were said to have had annual physical examinations whereas assessment times in fact ranged from 2 months to 6 years. Because of all these flaws, said the committee, "conclusions linking the efficacy of these therapies to growth and development are not warranted."

This report, completed in August 1986, was reviewed along with raw data by a committee of three outside researchers: Robert W. Berliner of Yale University, Gustav Schonfeld of Washington University, and Robert B. Uretz of the University of Chicago. They agreed that the study was not prospective and that "no meaningful interpretation of the results is warranted."

Glueck has defended himself in a 303-page rebuttal that he delivered to the university last November. Glueck maintained that the studies were indeed prospective, citing opinions to that effect from five researchers to whom he had sent copies of the article in the course of preparing his response.

He admitted to "some errors and inconsistencies" but contended that these "were random, not intentional." Part of the problem, he said, was that notebooks containing study data had been put in storage and could not be found at the time data were being analyzed, so he was forced to rely on data from patient charts, which were later found to be incomplete.

Glueck defended the qualitative data on maturation and school performance as being "summarized from a believable data base" in notebooks and charts, as well as his "intimate knowledge" of the patients. He told *Science* that these data were "a very minor part of the paper" and that the committees placed "a huge, perhaps disproportionate, amount of emphasis" on them. He said that in retrospect, "perhaps a better word would have been 'clinical impressions' or 'anecdotal clinical impressions.' "

Glueck said the data were reanalyzed after the notebooks were found (after publication of the *Pediatrics* paper), and that a reanalysis with revised data "shows that the fundamental results and conclusions reported in the paper are valid."

Glueck pleaded "severe work load overcommitment" as the principal reason for the flaws in the study. He said he was working 70 to 80 hours a week and was principal investigator on five other major studies in addition to clinical and administrative responsibilities. "It is my firm belief that this flawed paper was an isolated, aberrant fluke."

The university committee was unsympathetic with Glueck's response and said it "does not materially alter" its findings. It pointed out, for example, that the researchers who thought the study was prospective did not have access to any of the raw data. The committee made clear its disappointment with Glueck, noting that he failed "to objectively consider the suggestions and criticisms of his colleagues and peers" before the paper was published. It expressed "dismay" at his "apparent lack of recognition of the seriousness of his action."

Glueck stuck to his guns in a "surrebuttal," adding that "the unintentional errors are a humbling aberration. . . . "

Glueck is described by one colleague, Peter Kwiterovich of the Johns Hopkins University School of Medicine, as "a very energetic investigator . . . aggressive and hard-driving." He suggests that, in view of the current intense interest in cholesterol, Glueck may have been overhasty. "I think Glueck had this data and he was anxious to get it published."

According to Donald Harrison, senior vice president at the university's Medical Center, the university committee is still looking into possible problems with regard to the other studies in which Glueck has participated.

In addition to the 2-year debarment, the NIH committee recommended that Glueck be barred from serving on peer-review committees for 5 years and that he "immediately retract or issue a clarification" of the *Pediatrics* paper. It also said that notification of the investigation should be sent to editors at Elsevier-Australia, which has a manuscript based on the study; *Pediatric Research*, where Glueck submitted a paper based on the reanalyzed data, and the *New England Journal of Medicine*, where he published a letter referring to the study.

The NIH is currently auditing Cincinnati projects in which Glueck was involved. According to Mary Miers, the NIH misconduct policy officer, these include a National Heart, Lung and Blood Institute contract for lipid research that has involved the expenditure of $12.5 million since 1972, and a $1.5-million annual grant from the Division of Research Resources to the General Clinical Research Center.

Glueck, a member of one of Cincinnati's most prominent families (his father was president of Hebrew Union College), is now director of the Cholesterol Center at the Jewish Hospital of Cincinnati. The hospital says Glueck "has a distinguished reputation both on a national and international basis," and it is "privileged" to have him.

Glueck says he is likely to appeal the NIH finding once he receives formal notification. ■ CONSTANCE HOLDEN

British Space Chief Quits in Protest

The head of Britain's space program, Roy Gibson, has resigned in protest at Prime Minister Margaret Thatcher's decision to reject his request for a significant increase in the British government's support for space research. The government's decision is likely to require Britain to drop plans for the construction of the polar platform which its space engineers had hoped to build as their contribution to the proposed U.S. space station.

Gibson, a former director of the European Space Agency, was brought in 2 years ago to head the British National Space Centre (BNSC), which was recently created to coordinate the space activities of different government departments. Gibson said last week that the immediate cause of his resignation was the government's refusal to provide an extra $11 million requested by ESA as Britain's contribution to the extension of design studies on a new launcher, Ariane V, and on Columbus, a set of hardware that will represent Europe's contribution to the space station.

The design studies should be completed for a meeting of space ministers in November, which is intended to reach a firm agreement on Europe's medium-term space plans. In particular, this meeting will have to address the fact that support for Ariane V, Columbus, and the space plane Hermes would require member states to double their space budget over the next 5 years.

The BNSC has supported this strategy, and had submitted plans to the Cabinet suggesting that Britain should approve such an increase in its space budget. Gibson's resignation follows a statement from Thatcher that, for the time being, there will be no increase in Britain's space budget, and that any extra funds will have to be found from the private sector (*Science*, 7 August, p. 597).

"This means that we are effecively out of both Columbus and Ariane V" a spokesman for the BNSC said last week. Previously, it had been hoped that the British government would provide about 15% of the funding for Columbus—and that in return British Aerospace would have received the contract for the construction of a polar platform that will operate from the space station. "We will not necessarily be excluded from Columbus forever. But once you drop out of a certain phase of a program, it is very difficult to get back in," the spokesman added. ■

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