ence," and as having indicated that an important reason for founding the institute, although not the only one, was to redress the balance.

Self-criticism of another sort was reflected in action on recommendations of an ad hoc committee set up to study the AMA's scientific sections and scientific program and relations with outside specialty organizations.

A board of trustees report published in the AMA *Journal* on 18 May noted that the "AMA's scientific program has suffered from the splintering effects of specialization and the competition from numerous other scientific meetings" and recommended a number of changes in rules and organization in the sections.

The scientific sections, taken together, comprise the AMA's Scientific Assembly, which was established in 1859. In earlier days, the papers and essays presented at the section meetings "provided the exclusive or principal forum for specialty postgraduate medical education," said the committee. But the report went on to note that attendance at section meetings has been dwindling markedly and suggested four causes: (i) "intensified competition from an increasing number of specialty societies; (ii) presentation of section programs of limited interest and debatable quality; (iii) inadequate administrative machinery to handle section activities; (iv) insufficient authority in the Council on Scientific Assembly to direct and control the planning, publicizing and staging of section programs."

What seems to have precipitated the reappraisal in the past year was the tendency of some sections to operate independently of the parent organization and to issue policy statements without consulting the House of Delegates or obtaining its approval. Membership in the sections has not been limited to those qualified on rigorous terms, and business sessions of some sections had been so poorly attended that control of the sections in a few instances had been taken over by "outsiders."

The ad hoc committee recommended that the control issue be solved by empowering the AMA board of trustees to appoint section officers. The House of Delegates turned down this recommendation but acted favorably on other changes, such as one that would restrict membership in sections to those clearly qualified in the specialties, and others that would strengthen the ties with the parent organization and improve liaison with specialty organizations.

The effect of this action has been to leave the basic organization of the scientific sections much as it was, but to serve notice on section officers that unless they rejuvenate their scientific programs and tighten the reins on procedures, more changes will be made.

—JOHN WALSH

American Council on Education: Conference Designed to Illuminate The Ins and Outs of Grantsmanship

Last week in Washington the American Council on Education sponsored a Conference on Federal Programs for Colleges and Universities which, in essence, provided a basic training course for institutions not currently involved extensively in these programs but interested in learning how to do it themselves.

Upward of 450 college and university administrators, business officers, and faculty members attended the 2 days of meetings at the Mayflower Hotel, and council officials estimate that half of these represented institutions with decidedly limited experience in the art of federal grantsmanship.

A fair estimate seems to be that 90 percent of federal funds for research and fellowships go to 100 institutions among the 2000-odd universities and colleges (including junior colleges) in the United States. Federal money for fellowships, research, and faculty development is concentrated in those institutions which offer graduate programs. But many colleges which provide only undergraduate training have participated in the program of federal loans for college dormitories and the National Defense Education Act's undergraduate loan program and would like to explore further opportunities.

Lack of helpful information on opportunities to participate in federal programs has been one problem facing the novices, and the ACE conference, organized by the council's commission on federal relations, was designed to mitigate that problem.

The stress was on practice rather than theory in such panel discussions as the one forthrightly titled "developing effective proposals for submission by institutions and individual faculty members." In ten subdivided information groups the conferees were able to confront representatives from the agencies that finance the government's major programs affecting higher education. The main speeches were given by Commissioner of Education Francis Keppel and, fittingly, by Representative John E. Fogarty (D.–R.I.), who presides over the House Appropriations Subcommittee, the fount from which have flowed the funds to make the National Institutes of Health a billion-dollar-a-year research and education operation.

No definite plans have been made, but council officials say it is likely that the proceedings of the conference will be published this fall.—J.W.

Krebiozen: Nearly a Decade of Controversy Spent in Pursuit of "Fair", Government-Sponsored Test

This is the second of three articles on the Krebiozen controversy.

From 1951 to 1954, Krebiozen, as an experimental drug, had been distributed free to physicians requesting it for use on patients with advanced cancer. In April 1954, the drug's producers—at that time the Duga Biological Institute, later Promak Laboratories, both principally owned by Steven Durovic—moved to get commercial status by filing a New Drug Application with the Food and Drug Administration. Krebiozen's first run-in with the government not only reflected the ambiguities of its past but presaged the complexities of its future.

The application was denied, partly on the grounds that it was incomplete, but mainly on the argument that Krebiozen was a biological rather than a hormone, and thus subject to the licensing provisions of the Division of Biologic Standards of the Public Health Service rather than to FDA. The importance of the difference is that FDA at the time required only proof of safety, not of efficacy, while the PHS (which has jurisdiction over viruses, serums, toxins, and analogous products) requires both, and that unlike FDA's rulings, PHS rulings cannot be appealed. Krebiozen's sponsors disagreed on scientific grounds with this classification of the drug and have never applied to Biologic Standards. The jurisdictional uncertainties, never resolved, were mainly responsible for the blank check that FDA has given Krebiozen during the intervening years and which its sponsors now claim amounts, in effect, to a sanction.

After the application was rejected, the Krebiozen Research Foundation—the organization responsible for distributing and evaluating the drug—began seeking "donations" from patients receiving it. Estimates vary, but according to Ivy, between ½ and ⅓ of the approximately 4200 patients who have received Krebiozen have paid for it. Prices have changed over the years; the current rate is $9.50 per dose. The legality of these procedures is currently under FDA scrutiny, but they do not appear to have been prohibited by the drug laws that were in effect at the time.

From the relatively quiet recesses of the Food and Drug Administration, Krebiozen moved back into the headlines—and onto the editorial pages—not as a scientific but as a civil liberties issue. Learning that his former antagonist at the University of Illinois, George Stoddard, was describing his view of the events there in a book to be called "Krebiozen: The Great Cancer Hoax," Ivy, in the fall of 1954, obtained a temporary pre-publication injunction against the publisher, Beacon Press. The injunction was fought through to the Massachusetts Supreme Court and finally dismissed—but not until an ugly question of censorship had further clouded the Krebiozen record. Publication was delayed for a time, the manuscript was apparently revised a good deal, and the offending "Hoax" in the title was changed to the more humble "Mystery," but the changes were not sufficient to forestall a $350,000 libel suit which Ivy promptly initiated against Stoddard in Chicago. The legal issue predictably became entangled with the scientific evaluation of Krebiozen, and both—though in slightly different senses—are still pending.

Since 1957 the sponsors of Krebiozen have been skirmishing around the fringes of the scientific community, campaigning for a "fair test" for the product which they still believe to have been unfairly boycotted, if not the object of an outright conspiracy. In response to popular pressures that had implications for its own pocketbook, the American Cancer Society in 1958 expressed an interest in sponsoring a test of the drug, but the negotiations quickly collapsed; the main burden, since then, has been carried by the government's National Cancer Institute (NCI).

Negotiations between the Krebiozen Research Foundation (KRF) and the Cancer Institute have been carried on sporadically since the summer of 1958, most often stemming from popular or political pressures rather than from NCI's scientific initiative. In August 1958, at about the same time that NIH appropriation hearings were going on, Senator Paul Douglas proposed the selection of an arbitration committee to design and conduct a test of Krebiozen. One member of the committee was to be selected by NCI, one by KRF, and a third—a biostatistician to serve as chairman—by the two groups jointly. Despite considerable uneasiness on the part of NCI, discussion was opened. It quickly faltered on two questions: (i) whether Ivy would be a permissible member of the committee, and (ii) whether the material the Krebiozen Research Foundation agreed to submit was to serve as a basis for a test, as Ivy wanted, or as a basis for deciding whether a test was warranted, as the Cancer Institute wanted. To NCI, the insistence that Ivy supervise the planning and conduct of a test seemed incredible, since he was avowedly partisan. NCI interpreted the demand as a delaying tactic, and all the public and political noise-making as a stalling device to scare off the regulatory agencies and thus make continued distribution possible. To Ivy, on the other hand, exclusion from the committee, and the absence of a commitment from it to perform a test, meant that Krebiozen was once again to be subjected to a second-hand review by researchers who would lack the benefit of his own extensive experimentation. In February 1959 Ivy wired John Heller, the NCI director with whom he had been dealing, "We shall never again give any committee the opportunity of discrediting Krebiozen without first having formulated the criteria which will insure the performance of a valid and fair test. We do not want the opinion of a committee; we want a fair test." The negotiations collapsed.

More promising negotiations were opened in October 1960, following the appearance of a series of articles on Krebiozen in the New York *Post*. Shortly after his appointment as NCI director, Kenneth Endicott met privately with Ivy and Durovic; it was agreed that they would submit to NCI an analysis of their accumulated data on Krebiozen. According to the NCI version, the data were to be a basis for determining whether a test should be made; according to Ivy, it was to serve as the basis for such a test. This confusion did not become apparent till later, however, and in the interim more pressure was placed on NCI to conduct such a test by the intervention of the Illinois judge to whose lot had fallen the libel suit between Ivy and Stoddard. Although, in the libel charge against Stoddard, lawyers on both sides had agreed that only Ivy's professional conduct, and not the efficacy of Krebiozen, was at issue, Judge Julius Miner felt the case rested on evaluation of the drug, and in April 1961 he wrote to then Secretary of Health, Education, and Welfare Ribicoff asking for a test. Ribicoff's reply casts doubts on whether HEW's downtown branch knew what its uptown branch was doing, for the Secretary did not mention the likelihood of an NCI test. He did, however, mention that Durovic had filed a second New Drug Application the month before.

Durovic's second attempt to put Krebiozen on a commercial footing increased, rather than reduced, the intricacies of the controversy, and has remained to haunt the disputants. Although the Food and Drug Administration regards the application as having been officially rejected in June 1961, Ivy and Durovic have questioned the legality of the procedure followed and have indicated that for some purposes, at least, they regard the application as having become effective. Litigation would be needed to settle the point definitively, and the case would rest on technicalities, not the substantive adequacy of Durovic's application. So far, the dispute has functioned as a reserve force in the Krebiozen arsenal, and is drawn into battle only when the drug's experimental status appears threatened.

A "Fair Test" for Krebiozen?

In September 1961 Ivy and Durovic returned to the National Cancer Institute with the fruits of nearly a year's labor over their data—an 820-page draft analysis of their results on 4000 patients, and a manuscript to be submitted for publication in the NCI *Journal*. They also brought a small (and disputed) amount of Krebiozen—presumably between 7 and 10 mg. But the high hopes genuinely held on both sides that the Krebiozen controversy could at last be resolved were quickly dissipated.

The material submitted by Ivy in order, he thought, to facilitate the design of a clinical test appeared to re-

viewers at the Cancer Institute shockingly inadequate even to establish whether the drug was fit to be tested on human patients. Within a few months the manuscript submitted to the *Journal* had been rejected, and further consideration of proposals for a test tabled until more data could be supplied. The old question of whether Krebiozen was being justly treated by the scientific community was back again in full force. What was the cause of the trouble?

If there is reason to doubt that Ivy's data was scientifically inviolable, there is also reason to doubt that it was reviewed by NCI with a very sympathetic eye. Although the Institute's letters to Ivy and Durovic (7 and 8 March 1962) stressed, among other things, the inadequacy of prior toxicity and other studies on animals, the unreliability of the bioassay used (tests on breast cancers), and the uncertainty about Krebiozen's chemical nature, or its reproducibility, high NCI officials, in private conversation, have cast some doubt on the validity of their own objections, and on whether more is being demanded of Krebiozen than of some of the other hundreds of thousands of anticancer substances that the Institute regularly screens and, in many cases, tests on human patients. The human bioassay, for instance, while not regarded as satisfactory, is far from unique in the history of drug experimentation; Krebiozen has generally been conceded to be nontoxic (although this has not been independently established); Krebiozen would not be the first drug (nor the first tested at NCI) to be active on human cancers but not on animal cancers; and finally, an NCI official closely involved with the case stated that enough information had been revealed about the method of extracting and manufacturing Krebiozen for the Institute to produce (and presumably analyze) the substance itself. This would in no way resolve the controversy, since it could always be claimed that the batch produced was not identical to the batches with which Ivy and Durovic claim to have achieved their results; but it is an interesting comment on the validity of the NCI argument that Krebiozen is still too mysterious a substance to justify its use in human patients.

On the other side, however, and despite the fact that Ivy's data were not intended to establish the efficacy of Krebiozen but only to serve as a basis for tests that would do precisely that, it must be said that Ivy's scientific house was not in very good order, and his data did not make the Institute's task any easier. Taken separately, none of the elements of Ivy's report was unprecedented; but the separate unorthodoxies when added up appeared monumental, and left the Institute with the dizzy feeling that Krebiozen could simply not be pinned down in any reliable way. Some sense of the NCI's frustration in dealing with one of its former advisers, a man who officials felt should clearly "know better." can be gleamed from the letter to Ivy from H. B. Andervont, scientific editor of the Cancer Institute's *Journal*, rejecting his manscript (1 December 1961). After three pages detailing his reasons for regarding the manuscript as inadequate, Andervont closed with a paragraph that is a cross between a plea for scientific orthodoxy: "The manuscript differs from most scientific presentations in several respects. It does not contain an introduction in which the author refers to previous investigators who were interested in stimulating RES [the method of obtaining Krebiozen from horses] to ascertain whether it is involved in the growth of tumors. It does not contain a section of materials and methods for defining clearly the preparation of Krebiozen, the response of patients, the technique for collection and analysis of data procured from physicians, and the criteria used for their evaluation. It does not contain a discussion of results in relation to other kinds of cancer treatment. A conclusion is found on page 80 of a paper consisting of 120 pages."

The misunderstandings—partly petty disagreements over form, partly deep disagreements over substance—all sprang from the initial confusion over whether an NCI test had been absolutely, or only conditionally, promised. The refusal to conduct a test on the basis of the data supplied appeared to Ivy and Durovic as treachery; to the Cancer Institute, the pressure to test on human patients a substance about which it still felt so uncertain threatened its scientific and moral integrity. Both sides, however, though they suspected each other of the worst possible motives, were unwilling to give up the idea of a test altogether, and for different reasons both began to seek the aid of other government agencies in obtaining some of the data in dispute.

As far as NCI officials were concerned, the inadequacy of the material submitted suggested that Krebiozen's sponsors simply did not have the evidence to support their claims, and they began to press the Food and Drug Administration to determine whether Krebiozen was being "investigated" in a clinical sense, at all or merely distributed for commercial purposes. At the same time, in his reply to the Institute's rejection of his data in July, 1962 (strategically withheld until NIH appropriation time again, when it appeared simultaneously as a letter to Endicott and as an entry, by Senator Douglas, in the *Congressional Record*) Ivy explained that some of the material NCI wanted—mainly extensive case histories of patients on Krebiozen—had been impossible to obtain.

Ivy attributed his own inability to collect the records mainly to the inhibitions of physicians in admitting that they had administered a drug that had been frowned on by organized medicine, and in part simply to the financial burdens the task had posed. Although he did not agree that the data was crucial to the proposed NCI test, he did suggest that lack of such data had "impeded our study of the past 12 years," and he, too, suggested that the government use its power to get the records from hospitals and private physicians.

With requests from both sides on its hands, the Food and Drug Administration could hardly avoid initiating an investigation. After a few more minor skirmishes, an investigation into both the commercial and clinical history of Krebiozen was begun in March 1963. Things were at this stage when the unresolved controversy collided with new drug laws to produce the Krebiozen panic of early June.

—ELINOR LANGER

Announcements

A department of **pharmacology** will be activated 1 July at Wake Forest College's Bowman Gray school of medicine. It was formerly part of the department of physiology and pharmacology. J. Maxwell Little, formerly head of the pharmacology section in the combined department, is chairman of the new facility.