PHS Grant-Supported Research With Human Subjects

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A POLICY on grant-supported research with human subjects was announced in a memorandum, dated July 1, 1966, from Surgeon General William H. Stewart to heads of institutions receiving Public Health Service grants. The first communication on this subject was transmitted in February 1966, but it applied only to research grants and research training grants. The July statement revised and simplified procedures and extended the policy to virtually all grants and awards of the Public Health Service.

The Policy

INSTITUTIONAL RESPONSIBILITY. The policy emphasizes that safeguarding the rights and welfare of human subjects is a responsibility of the institution to which the grant is awarded. This statement does not imply a passive attitude on the part of the Public Health Service. On the contrary, the policy explicitly states that nothing should inhibit the Service's staff, advisory groups, or consultants from identifying concern for the welfare of human subjects or questioning an application if the gravity of risks so indicates.

Dr. Confrey, director, Division of Research Grants, National Institutes of Health, Public Health Service, presented this paper at a meeting of the Council for International Organizations of Medical Sciences, Paris, France, October 7, 1967.

INDEPENDENT REVIEW. The Public Health Service requires, before initiation of an investigation, review of the judgment of the investigator by a committee of institutional associates which addresses itself to (*a*) the rights and welfare of the individual, (*b*) the appropriateness of methods used to obtain informed consent from the subject, and (*c*) the risks and potential benefits of the investigation.

To enhance the probability of an independent determination, the policy specifies that members of the committee have no vested interest in the specific project. The institution may use staff or consultants, provided that the group possesses competence to comprehend the scientific content of the proposed research and other competencies pertinent to the judgments. Written records of group review are required as well as documentary evidence of informed consent.

SURVEILLANCE AND ADVICE. Since research protocol often changes in the course of investigation, institutions are required to provide mechanisms to deal with emergent problems and proposed changes during the investigation. Moreover, institutions are expected to provide advice for investigators on safeguarding the rights and welfare of human subjects.

FACILITIES. The institution has the responsibility to provide whatever professional attention or facilities may be required for the safety and well-being of human subjects.

ASSURANCE. As evidence of its acceptance of

these conditions, the institution (university, medical school, research institute, hospital, or other) is requested to submit to the Division of Research Grants, National Institutes of Health, a written assurance with appropriate attachments. Briefly, these documents are expected to encompass several points, among them: (*a*) agreement with the principles of the policy, and (*b*) a description of the method of review, the competencies represented in the review committee, the administrative mechanisms for surveillance and advice, and "the manner in which the institution will assure itself that the advice of the committee . . . will be followed."

If changes are made in institutional policies, procedures, or committee competencies, the institution is required to inform the Public Health Service.

On December 12, 1966, the Surgeon General elaborated on the July memorandum, primarily to clarify responsibilities for research in the behavioral and social sciences. The clarification emphasizes the following points.

COMMUNITY LAWS. The grantee institution is responsible for assuring that the research is "in accord with the laws of the community in which the investigations are conducted and for giving due consideration to pertinent ethical issues."

SEPARATE GROUPS. Due to misunderstanding of the original statement, several institutions questioned the rationale of establishing one review group for all research disciplines. Accordingly, the clarification emphasizes the option of designating separate review groups for particular areas.

DISTINCTIONS IN RESEARCH. In recognition of significant differences in the effects of research on human subjects, the statement reflects special concern about procedures that induce an altered state potentially harmful to a subject's personal welfare; for example, surgical procedures, administration of drugs, or strenuous physical exertion.

There is, the policy states, much behavioral research in which no personal risk is involved. Nonetheless, sensitive questions remain as to the voluntary nature of the subject's participation, maintenance of confidentiality of information, and protection of the subject from misuse of the findings.

To illustrate such research, the statement cites the observation of subjects and the administration of tests, questionnaires, and surveys of personality. Although voluntary participation, confidentiality, and propriety in use of findings are still germane, "such procedures may . . . not require fully informed consent of the subject or even his knowledgeable participation." In such instances, however, specific documentation is necessary.

JUDGMENT. This element is explicitly alluded to in the clarifying statement. In research such as studies of human learning or social perception, the effects on the subject may be transitory or permanent, "but they must be judged clearly not to be harmful or not to involve risk of harm."

AGE AND COMPETENCE. Concern for protection of the subject and for voluntary participation becomes most critical, the policy states, when the subject is not of age or competence to make an adequate judgment in his own behalf.

REVIEW-GROUP DECISION. The December statement concludes with the observation that each project must be considered individually. Moreover, based on its scrutiny of the proposed research, the local review group can decide which issues are germane and, where they are germane, ascertain the adequacy of provisions for protecting rights and welfare of subjects, for obtaining informed consent, and for weighing risks and benefits.

Principles

In formulating its policy on grant-supported research with human subjects, the Service has attempted to reflect certain principles.

AVOIDANCE OF EXTREMES. Theoretically, the range of choices available in such policy formulation extends from a decision to exercise no Federal role to a decision to pervade and dominate all local judgments.

To contrast these extremes, an advocate of minimal or no Federal role would be likely to emphasize, say, the professional integrity characteristic of scientists engaged in clinical or behavioral research. The proponent of maximal Federal responsibility and control might submit that a researcher is often too preoccupied with discovery to pay adequate heed to protection of the research subject.

In the light of public attention to this problem and the magnitude of research supported by public funds, it is not feasible for any Federal agency to avoid some measure of responsibility—nor would Federal officials consider such an attitude proper. At the other extreme, surveillance by the Federal Government of research procedures and their ethical implications relating to tens of thousands of grants and contracts is correspondingly infeasible, to say nothing of its propriety.

In what segment of the continuum, then, does the wise course of action lie? The Public Health Service assumption is that wisdom in such matters is most likely to be found a considerable distance from the extremes. Moreover, since this sensitive issue will be in flux for some time to come, and progress and understanding will be accomplished incrementally, the precise position of the Government cannot be fixed on a once-and-for-all basis. Rather than attempt to establish an inflexible role—be it one of mere exhortation or rigorous surveillance—the Service considers another attitude, that of complementary roles, more likely to produce fruitful results.

COMPLEMENTARY ROLES. Among the principal agents involved in this situation, as it pertains to federally supported research activities, are the granting agency, the grantee institution, and the individual investigator or clinician. Just as the Government's role should avoid extremism, the respective roles of all parties should, when feasible, be differentiated and complementary.

Thus, it would seem appropriate for the Government agency to identify general standards, first having drawn on the expertise developed by professional societies and other organizations—in this case, medically and scientifically oriented groups, hospitals, experienced research institutions, and sources of legal advice. Second, since mere exhortation is limited in utility, it is proper for the agency to require adherence to these standards. Third, the agency should recognize its responsibility not only to proclaim and review the effects of such proclamations but, perhaps more importantly, to pursue a positive role of providing guidance, advice, and assistance to its clientele. Finally, however strong the urge, the agency should resist all inclination to write detailed manuals of procedures, attempting to anticipate every conceivable question and to translate these into elaborate instructions. The agency is responsible for stating general requirements as clearly and unambiguously as possible, but should not try to tell an institution or investigator in meticulous detail how to meet these requirements.

The role of the institution should include the unequivocal acceptance of responsibility for meeting governmental standards and for establishing procedures to implement the standards. An academic institution or hospital is expected to review projects for ethical implications just as it now reviews other elements, such as budget items, of a project. The institution as such, or a component thereof, seems to be the proper agent for overseeing research programs involving human subjects and for providing advice to faculty and staff.

Ultimately, the research scientist is responsible for the quality of the investigation. He designs the experiment or the survey questionnaire. He is, for instance, most aware of whether a research subject really understands the proposed experimental procedure and its possible consequences. As the Medical Research Council of Great Britain observed (*1*):

> All who have been concerned with medical research are aware of the impossibility of formulating any detailed code of rules which will ensure that irreproachability of practice which alone will suffice where investigations on human beings are concerned. . . . [The] considerations involved in a novel procedure are nearly always so technical as to prevent their being adequately understood by one who is not himself an expert. It must, therefore, be frankly recognized that, for practical purposes, an inescapable moral responsibility rests with the doctor concerned for determining what investigations are, or are not, proposed to a particular patient or volunteer.

The principle of complementary roles encompasses all forces in society potentially capable of contributing to better understanding of the scope and limits of research on human subjects.

RECOGNITION OF DIVERSITY. A third principle reflected in the Public Health Service policy is the awareness of significant differences in institutional settings, types of research, subjects, and investigators. Such differences limit the likelihood of success in formulating rules common to diverse situations (*2*).

The policy applies to medical facilities, many of which have broad experience in medical care and clinical research. Precedent cases are available, the staff is experienced and knowledgeable in the ethics of medical practice, and there is a sensitivity to moral and legal issues. One begins with a presupposition of sophistication in such facilities and tends to assume that present methods will require little modification to conform to Public Health Service requirements. On the other hand, some facilities can draw on far less experience and will likely require considerable assistance in developing procedures for safeguarding patient welfare. A nonmedical setting may raise different problems, since the staff may lack the experience of medical practice and its associated ethical and legal implications.

Analogous differences exist in respective types of research—medical, social, and behavioral. In medical research, a subject may face potential benefit juxtapositioned with risks. In some behavioral research, neither benefit nor risk to the subject may be at issue, but confidentiality and protection against misuse of findings may be critical.

Circumstances differ relative to the kinds of subjects—the seriously ill, normal volunteers, prisoners, children, or mentally incompetent. Similarly, there are distinct contrasts in experience, judgment, and attitudes of researchers in various scientific disciplines.

All such variables must be considered in policy formulation, yet the variations do not allow simple reduction to a concept of, say, "the welfare of subjects." Accordingly, the policy must be expressed in a manner that will accommodate differences as well as resemblances among situations. It must be sufficiently general to encompass diversity while avoiding a degree of abstraction that makes it platitudinous, hence vacuous.

THE CONCEPT OF A GRANT. Another influence on the form of the policy on human research is the fact that the Public Health Service has traditionally viewed the grant relationship as being quite special. The agency has not contracted for a tangible product, to be produced under rigorously specified terms and conditions. On the contrary, a grant is interpreted as a form of financial assistance to an institution on behalf of an investigator so that he may pursue a problem in which he is interested and which coincides with an area of biomedical research relating to a national objective. Given this concept, the agency will endeavor to optimize the conditions conducive to the advancement of knowledge, including maximal freedom of inquiry. This relationship does not entail Federal retreat from responsibility; but, as stated previously, it does presuppose an acute awareness of the scope and appropriate limits of Federal action.

Experience With Policy

STATISTICS. In fiscal year 1966, the Public Health Service awarded approximately 32,000 grants for research, training, demonstration, health services, and construction, totaling about $1.6 billion. Grantees (universities, hospitals, departments of health, medical schools, and others) numbered about 3,000.

As of July 1, 1967, assurance statements had been received from more than 1,000 of the grantees whose projects include human subjects. The majority of the assurances have been approved, and the institutions identified as eligible for Public Health Service support, insofar as the protection of human subjects is concerned. Since November 1, 1966, no grant for a project with human subjects can be made to an institution not so identified.

Although no institution has as yet refused to accept the Service's requirement for institutional acceptance of responsibility, in some instances the assurances submitted are incomplete or otherwise unacceptable. Such circumstances have led, not to an outright rejection of an institution, but to additional correspondence with the grantee in order that the source of the problem may be identified and eventually corrected.

RESPONSES. Academic institutions and other organizations have responded favorably to the Surgeon General's announcement. Many respondents have stated that the policy is reasonable and that it correctly emphasizes the proper locus of responsibility. Whether such responses are construed as endorsement of the policy or as reluctance to risk jeopardizing grant support, the fact remains that few grantee institutions have publicly expressed opposition to the Public Health Service stand.

As with the introduction of any new public policy relating to a complex issue, the announcement of the Service's requirements on human research has evoked questions, prompted suggestions, and elicited some criticism. The following questions are illustrative.

Why should foreign institutions conducting research projects be subjected to U.S. requirements? The policy applies, of course, to those institutions abroad that are engaged in projects supported, in whole or in part, by Public Health Service grants and awards. The question of including or excluding these institutions has raised issues, some of which go beyond the normal difficulties of language. Cultural differences, for example, make it difficult for a hierarchical society or organization to understand the need for "a committee of institutional associates" with the authority of decision. Dilemmas arise in relationship to foreign institutions. If the requirements are less stringent than for U.S. organizations, this seems to imply less concern by the U.S. Government for the welfare and rights of research subjects abroad. If, on the other hand, the same terms and conditions are made applicable to foreign projects supported by U.S. funds, this can be construed as an infringement on the prerogatives of foreign governments and their institutions. Since review standards should not be determined by national boundaries, it was decided to have similar requirements for domestic and foreign institutions, and, thus far, there has been no less cooperation from the latter.

What is the prescribed composition of a review group? In accord with the principles stated previously, the Public Health Service has deliberately avoided specifying the composition of review groups. Rather, the selection should be a responsibility of the institution, and will likely vary with diverse circumstances. Many groups include legal advisers, and some include lay members of the community, clergymen, and philosophers as well as research-oriented personnel.

Should the group review be conducted before an application is submitted to the Public Health Service or after an award is made? The Public Health Service requires that "prior to inception of each course of investigation, objective decisions be made. . . ." If the review is made before the application is submitted, it may be moot if the project is disapproved or not funded. If the review is made by an institution after receiving an award, and the group then expresses its disinclination to have the project proceed, this too can present problems. The position of the Service is to encourage such review over and beyond the relationship to specific grant applications. It is assumed, in other words, that institutions and their staffs will continue to address themselves to these issues, whether or not Federal financial assistance is sought in support of projects.

Why does the Public Health Service not leave to professional organizations the formulation of standards relating to human research? There are two aspects to this question: the formulation of ethical codes and the formulation of administrative standards for implementation of the codes. Under the principle of complementary roles, the Service expects professional societies to continue their efforts at devising and refining such codes. The Government as well as other components of society will benefit from these endeavors. Until such time as these codes are widely adopted and their objectives realized, the Service will continue its primary role of highlighting problems and requiring—albeit in general terms—administrative steps necessary to minimize such problems.

If the institution must convince the Public Health Service of the adequacy of its manner of protecting human rights, does not this action preempt institutional prerogatives in such decisions? The key distinction here is the difference between "manner" and "decisions." Foremost in the interest of the Service is the mechanism by which proposals are reviewed locally and advice given to investigators. If this "manner" is appropriate, there should be no need for anyone outside the institution to intrude on individual decisions.

But the Public Health Service still "intrudes"—do not its study sections, councils, and staff still retain the right to disapprove an application on ethical grounds? Clearly, the local institution and its faculty should have better insight, in depth, into the circumstances—the research, the subjects, the protocol, the hazards. On the other hand, national panels of scientists

bring a broad viewpoint based on experience with similar research proposals derived from many institutions. Nonetheless, this national review is intended to provide merely one additional checkpoint. Given a project proposal of scientific merit, it is unlikely that any panel will vote outright disapproval on ethical criteria. Instead, the panel will probably recommend a site visit, during which the ethical issue can be discussed locally with those concerned. Moreover, as local competency in handling such matters increases, there should be a concomitant decrease in questions raised at the national level.

Will not faculty refuse to serve on local review groups? On the contrary, research scientists, clinicians, and others are demonstrating their willingness to deal with these problems. In this, as in other matters requiring a collective judgment, the Public Health Service has seen little evidence of reluctance by individuals to participate in the decisions. Rather, scientists tend to share the conviction of the Director, National Institutes of Health, that "faculty members who devote time and effort to increasing the ability of their institutions to govern themselves are performing an important service for science and its academic matrix" (*3*).

Can surveillance really be conducted without establishing a closed-circuit television system and monitoring each experiment? The use of the word "surveillance" in the policy is probably unfortunate. Certainly, the intent is that of mutually shared recognition of a problem, rather than institutional policing of staff. Hopefully, the climate will be that of advice, counsel, and mutual respect.

What is meant by "informed consent," "voluntary participation," "harmful effects," "rights and welfare of human subjects," "invasion of privacy"? Many of these key terms lack rigorous definition or are incompletely defined for purpose of general application. Regulations of the Food and Drug Administration include a definition of "consent" (*4*). Some definitions will be further clarified as a result of legal action. At the same time, much progress can be expected from scholarly analysis of basic concepts. Wolfensberger (*5*), for example, has sorted out various levels of research, types of consent, and types of risk. The literature is expanding as a consequence of increased attention to the problem by lawyers, physicians, psychologists, sociologists, and philosophers. In the meantime, the Public Health Service has elected to use, as a point of departure, terms drawn from ordinary language and common usage, stipulating these as the operational definitions for a public policy.

The Future

At present, only a superficial analysis can be made of the effects of the policy on institutions and individuals conducting research with human subjects. The evidence thus far is anecdotal, but encouraging. Especially so are the elaborate descriptions of local procedures, submitted by hundreds of organizations, which reflect serious, conscientious effort. As a part of its technical assistance, the Public Health Service has duplicated copies of several plans and, with permission from the institutions that formulated the procedures, has provided these copies as prototypes to institutions requesting such information.

Now that a general principle has been enunciated, the Service intends to serve as catalyst in attaining better understanding of this social problem. Accordingly, the National Heart Institute has awarded a grant to the American Academy of Arts and Sciences to support an inquiry into the moral and ethical basis for research involving human subjects. The considerations and conclusions of the study will be published in *Daedalus*, a journal of the Academy.

As evidence of the increasing interest and attention to the subject, the U.S. Office of Science and Technology recently released a report on "Privacy and Behavioral Research" prepared by a distinguished panel (*6*).

Among its conclusions and recommendations were the following:

> . . . Greater attention must be given to the ethical aspects of human research.
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> . . . Government must avow and maintain the highest standards for the guidance of all.
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> . . . The primary responsibility . . . must rest with the individual investigator, but Government agencies . . . should satisfy themselves that the institution which employs the investigator has effectively accepted its responsibility to require that he meet ethical standards.

. . . The decision cannot be made solely by the investigator, who normally has a vested interest in his own research program, but must be a positive concern of his scientific peers and the institution which sponsors his work.

. . . [The] methods used for institutional review [should] be determined by the institutions themselves.

It is reasonable to expect that many professional organizations and other interested groups will be giving attention to similar issues.

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(*4*) Food and Drug Administration: New drugs, consent for use of investigational new drugs on humans; statement of policy. [21 CFR, pt. 130] Federal Register 32: 118 (1967).

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(*6*) Office of Science and Technology: Privacy and behavioral research. U.S. Government Printing Office, Washington, D.C., February 1967.

Specially Bred Mosquitoes Eradicate Filariasis Carrier

A factor called cytoplasmic incompatibility is being used to control insect-borne diseases. Selective altering of the male's chromosomes in the geneticist's laboratory results in insects whose cytoplasm carries a factor that blocks sperm from fertilizing eggs. When such a male mates with a naturally bred female, nothing comes of their union.

The field trial of this technique in Okpo, a Burmese village 16 miles north of Rangoon, was directed by Prof. Hannes Laven, director of the Institute for Genetics at the Johannes Guttenberg University, Mainz, West Germany. He worked with the *Culex fatigans* mosquito, carrier of filariasis.

Dr. Laven, who 20 years ago discovered an incompatibility inherent in different strains of the same mosquito species, bred incompatibility into a strain of *C. fatigans* and released their laboratory raised male offspring at a rate of 5,000 a day in Okpo. At this rate enough insects were released to crush competition for the females from the local males.

Laven said that using Okpo as the proving ground for the genetic technique contributed to the trial's success. Mosquitoes can fly only about a mile, and the dry rice fields around the village put the settlement of 150 houses beyond the reach of outside mosquitoes. None of the *C. fatigans* eggs found in the 150- by 350-meter area hatched.

Insecticides have been used successfully against insects, but as insects develop resistance to them they become less efficient. Moreover, poisons are not selective and kill off other species in addition to the offending one. Genetic eradication, however, is almost 100 percent selective, according to Dr. Edward F. Knipling, director of the U.S. Department of Agriculture's Entomology Research Division, who was the pioneer in the use of the nonchemical strategy.

Another control method, developed by Knipling, centers on sterilization of the male insect with gamma radiation. It has been used to eradicate the screw-worm, a fly that is a cattle pest of the southeastern United States. Sterilization does not work well against the mosquito, however, because sterilized males do not compete for the females.

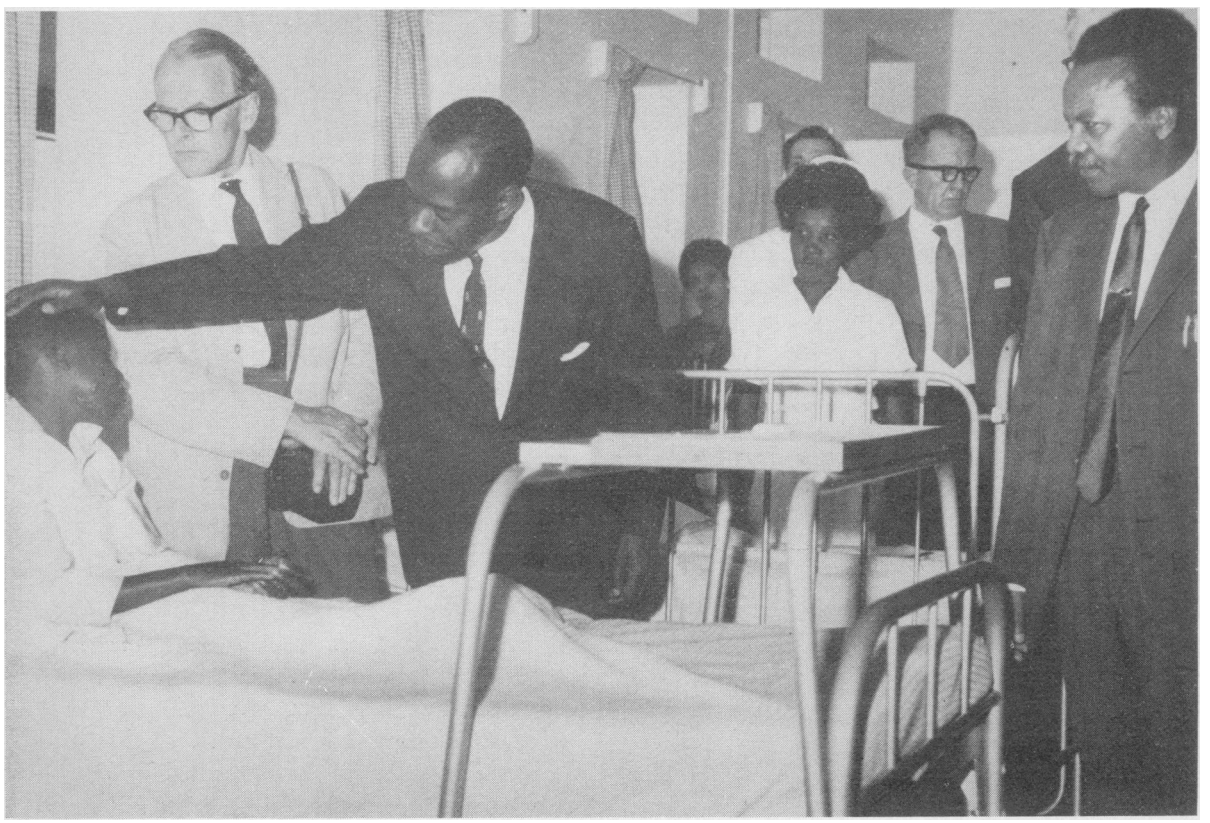
More than 120 million persons live in areas endemic for filariasis in India, and an estimated 5 million are affected clinically. Filariasis is a major public health problem for many other Asian countries. Eradication of the insect from a filariasis area need not be permanent, according to Dr. Rajindar Pal, a World Health Organization expert, who says that if the filariasis vectors can be eliminated for only a few years there would be nothing for the species to carry if it were reintroduced into the area.

Cooperative Venture To Study Cancers Common in Africa

Certain types of cancer common in Africa and of theoretical and practical interest to U.S. scientists will be studied by Public Health Service and African medical authorities. The study, a cooperative venture by the Service's National Cancer Institute and Makerere University College in Kampala, Uganda, is expected to take 4 years. Public Health Service support for the first year is $65,258.

Selected patients with lymphomas will be hospitalized at a new treatment center being established with Public Health Service assistance at Makerere University College. African children with a form of cancer called Burkitt's lymphoma will be included. This form of cancer occurs rarely in the United States, but may bear a relationship to the most frequently occurring cancer of American children, acute leukemia. Patients with Hodgkin's disease and Kaposi's sarcoma will also be studied.

The responses of African patients to drug treatment and stimulation of their immune systems will be measured and compared with responses of American patients under treatment at the National Institutes of Health's Clinical Center. Immune reactions and characteristics of blood and bone marrow will be evaluated in an effort to discover why many African patients seem to respond better to drug therapy than American patients. These findings will be correlated with a continuing National Cancer Institute study of environmental and genetic factors that may affect the development of lymphoma in an African and his response to treatment.



Dr. Denis Burkitt, discoverer of Burkitt's lymphoma, left, and Mr. J. W. Lwamafa, Minister of Health, Uganda, right, watch as Dr. Sebastian Kyalwazi, senior surgical consultant, Mulago Hospital, Uganda, examines a young patient.