FINAL REPORT
of the
Tuskegee Syphilis Study
Ad Hoc Advisory Panel

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

April 28, 1973

Dr. Charles C. Edwards
Assistant Secretary for Health
U.S. Department of Health, Education, and Welfare
Washington, D.C. 20202

Dear Doctor Edwards:

The final report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel is transmitted herewith. The Chairman specifically abstains from concurrence in this final report but recognizes his responsibility to submit it.

Sincerely yours,

Broadus N. Butler

Broadus N. Butler, Ph.D.
President
Dillard University

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

CHARTER

Tuskegee Syphilis Study Ad Hoc Advisory Panel to the Assistant Secretary for Health and Scientific Affairs

Purpose

To fulfill the public pledge of the Assistant Secretary for Health and Scientific Affairs to investigate the circumstances surrounding the Tuskegee, Alabama, study of untreated syphilis in the male Negro initiated by the United States Public Health Service in 1932.

Authority

The committee is established under the provisions of Section 222 of the Public Health Service Act, as amended, 42 US Code 217a, and in accordance with the provisions of Executive Order 11671, which sets forth standards for the formation and use of advisory committees.

Function

The committee will advise the Assistant Secretary for Health and Scientific Affairs on the following specific aspects of the Tuskegee Syphilis Study:

Determine whether the study was justified in 1932 and whether it should have been continued when penicillin became generally available.

Recommend whether the study should be continued at this point in time, and if not, how it should be terminated in a way consistent with the rights and health needs of its remaining participants.

Determine whether existing policies to protect the rights of patients participating in health research conducted or supported by the Department of Health, Education, and Welfare are adequate and effective and to recommend improvements in these policies, if needed.

Structure

The committee will consist of nine members, including the Chairman, not otherwise in the full-time employ of the Federal Government. Members will be selected by the Assistant Secretary for Health and Scientific Affairs from citizens representing medicine, law, religion, labor, education, health administration, and public affairs.

The Panel members will be invited to serve for a period not to extend beyond December 31, 1972, unless an extension beyond that time is approved by the Assistant Secretary for Health and Scientific Affairs. The Assistant Secretary for Health and Scientific Affairs will designate the Chairman.

Management and staff services will be provided by the Office of the Assistant Secretary for Health and Scientific Affairs.

Meetings

Meetings will be held at the call of the Chairman, with the advance approval of a Government official who shall also approve the agenda. A Government official will be present at all meetings.

Meetings shall be conducted, and records of the proceedings kept as required by Executive Order 11671 and applicable Departmental regulations.

Compensation

Members who are not full-time Federal employees will be paid at the rate of $100 per day for time spent at meetings, plus per diem and travel expenses in accordance with Standard Government Travel Regulations.

Annual Cost Estimate

Estimated annual cost for operating the committee, including compensation and travel expenses of members but excluding staff support, is $74,000. Estimate of annual man years of staff support required is one year at an estimated annual cost of $16,000.

Report

A final report based on the committee's investigation will be made to the Assistant Secretary for Health and Scientific Affairs. A copy of this report shall be provided to the Department Committee Management Officer.

The Tuskegee Syphilis Study Ad Hoc Advisory Panel to the Assistant Secretary for Health and Scientific Affairs will terminate on December 31, 1972, unless extension beyond that date is requested and approved.

FORMAL DETERMINATION

By authority delegated to me by the Secretary on September 29, 1969, I hereby determine that the formation of the *Tuskegee Syphilis Study Ad Hoc Advisory Panel to the Assistant Secretary for Health and Scientific Affairs* is in the public interest in connection with the performance of duties imposed on the Department by law, and that such duties can best be performed through the advice and counsel of such a group.

8/28/72	(sgd.) Merlin K. DuVal, M.D.
Date	Assistant Secretary for Health and Scientific Affairs

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

CHARTER

Tuskegee Syphilis Study Ad Hoc Advisory Panel to the Assistant Secretary for Health

Purpose

To fulfill the public pledge of the Assistant Secretary for Health to investigate the circumstances surrounding the Tuskegee, Alabama, study of untreated syphilis in the male Negro initiated by the United States Public Health Service in 1932.

Authority

The Panel is established under the provisions of Section 222 of the Public Health Service Act, as amended, 42 US Code 217a; the Panel is governed by provisions of Executive Order 11671, which sets forth standards for the formation and use of advisory committees.

Function

The Panel will advise the Assistant Secretary for Health on the following specific aspects of the Tuskegee Syphilis Study:

Determine whether the study was justified in 1932 and whether it should have been continued when penicillin became generally available.

Recommend whether the study should be continued at this point in time, and if not, how it should be terminated in a way consistent with the rights and health needs of its remaining participants.

Determine whether existing policies to protect the rights of patients participating in health research conducted or supported by the Department of Health, Education, and Welfare are adequate and effective and to recommend improvements in these policies, if needed.

Structure

The Tuskegee Syphilis Study Ad Hoc Advisory Panel to the Assistant Secretary for Health consists of nine members, including the Chairman, not otherwise in the full-time employ of the Federal Government. Members are selected by the Assistant Secretary for Health from citizens representing medicine, law, religion, labor, education, health administration, and public affairs. The Chairman is designated by the Assistant Secretary for Health.

The Panel members are invited to serve for a period not to extend beyond March 31, 1973, unless an extension beyond that time is approved by the Assistant Secretary for Health.

Management and staff services will be provided by the Office of the Assistant Secretary for Health which supplies the Executive Secretary.

Meetings

Meetings will be held at the call of the Chairman, with the advance approval of a Government official who shall also approve the agenda. A Government official will be present at all meetings.

Meetings are open to the public except as determined otherwise by the Secretary; notice of all meetings is given to the public.

Meetings are conducted, and records of the proceedings kept, as required by applicable laws and Departmental regulations.

Compensation

Members who are not full-time Federal employees will be paid at the rate of $100 per day for time spent at meetings, plus per diem and travel expenses in accordance with Standard Government Travel Regulations.

Annual Cost Estimate

Estimated annual cost for operating the Panel, including compensation and travel expenses of members but excluding staff support, is $74,000. Estimate of annual manyears of staff support required is one year, at an estimated annual cost of $16,000.

Report

A final report based on the Panel's investigation will be made to the Assistant Secretary for Health, not later than April 30, 1973, which contains as a minimum a list of members and their business addresses, the dates and places of meetings, and a summary of the Panel's activities and recommendations. A copy of this report shall be provided to the Department Committee Management Officer.

Termination Date

Unless renewed by appropriate action prior to its expiration, the Tuskegee Syphilis Study Ad Hoc Advisory Panel to the Assistant Secretary for Health will terminate on March 31, 1973.

APPROVED:

1/4/73	(sgd.) Richard L. Seggel
Date	Acting Assistant Secretary for Health

PANEL MEMBERS

Chairman:

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MEETINGS

TUSKEGEE SYPHILIS STUDY AD HOC ADVISORY PANEL

1. September 22, 1972
   Subcommittee Meeting on Charge III
   Holiday Inn – La Guardia Airport
   New York, New York
2. September 27, 1972
   Panel Meeting
   National Institutes of Health
   Bethesda, Maryland
3. October 25, 1972
   Panel Meeting
   National Institutes of Health
   Bethesda, Maryland
4. November 2, 1972
   Panel Meeting
   National Institutes of Health
   Bethesda, Maryland
5. November 30, 1972
   Panel Meeting
   National Institutes of Health
   Bethesda, Maryland
6. December 18, 1972
   Subcommittee Meeting on Charge I
   Subcommittee Meeting on Charge III
   National Institutes of Health
   Bethesda, Maryland
7. December 19, 1972
   Panel Meeting
   National Institutes of Health
   Bethesda, Maryland
8. January 24, 1973
   Subcommittee Meeting on Charge III
   55 East 52nd Street
   New York, New York
9. February 23, 1973
   Subcommittee Meeting on Charge I
   National Institutes of Health
   Bethesda, Maryland
10. March 1, 1973
    Panel Meeting
    Parklawn Building
    Rockville, Maryland
11. March 20, 1973
    Subcommittee Meeting on Charge III
    26 Federal Plaza
    New York, New York
12. March 28, 1973
    Panel Meeting
    National Institutes of Health
    Bethesda, Maryland

REPORT ON CHARGE I

April 24, 1973

Tuskegee Syphilis Study Ad Hoc
Advisory Panel

Acknowledgements

Subcommittee for Charge I

The Co-Chairmen wish to acknowledge the input of members of the subcommittee and panel members whose input and deliberations were essential to the final report for Charge I:

Members of the Subcommittee for Charge I

Mr. Ronald H. Brown
Dr. Vernal Cave
Mr. Barney H. Weeks
Dr. Jean L. Harris, Co-Chairman
Dr. Jeanne C. Sinkford, Co-Chairman

and

Mr. Fred Speaker, Panel Member

Also, our sincere appreciation to staff members who assisted in editing, typing and distributing the final report:

Dr. Robert C. Backus
Mrs. Bernice M. Lee
Mrs. Jacqueline Eagle

FINAL REPORT

TUSKEGEE SYPHILIS STUDY AD HOC ADVISORY PANEL

REPORT ON CHARGE I-A

Statement of Charge I-A: Determine whether the study was justified in 1932.

Background Data

The Tuskegee Study was one of several investigations that were taking place in the 1930's with the ultimate objective of venereal disease control in the United States. Beginning in 1926, the United States Public Health Service, with the cooperation of other organizations, actively engaged in venereal disease control work.[1] In 1929, the United States Public Health Service entered into a cooperative demonstration study with the Julius Rosenwald Fund and state and local departments of health in the control of venereal disease in six southern states[2]: Mississippi (Bolivar County); Tennessee (Tipton County); Georgia (Glynn County); Alabama (Macon County); North Carolina (Pitt County); Virginia (Albermarle County). These syphilis control demonstrations took place from 1930-1932 and disclosed a high prevalence of syphilis (35%) in the Macon County survey. Macon County was 82.4% Negro. The cultural status of this Negro population was low and the illiteracy rate was high.

During the years 1928-1942 the Cooperative Clinical Studies in the Treatment of Syphilis[3] were taking place in the syphilis clinics of Western Reserve University, Johns Hopkins University, Mayo Clinic, University of Pennsylvania, and the University of Michigan. The Division of Venereal Disease, USPHS provided statistical support, and financial support was provided by the USPHS and a grant from the Milbank Memorial Fund. These studies included a focus on effects of treatment in latent syphilis which had not been clinically documented before 1932. A report issued in 1932 indicated a satisfactory clinical outcome in 35% of untreated latent syphilitics.

The findings of Bruusgaard of Oslo on the results of untreated syphilis became available in 1929.[4] The Oslo study was a classic retrospective study involving the analysis of 473 patients at three to forty years after infection. For the first time, as a result of the Oslo study, clinical data were available to suggest the probability of spontaneous cure, continued latency, or serious or fatal outcome. Of the 473 patients included in the Oslo study, 309 were living and examined and 164 were deceased. Among the 473 patients, 27.7 percent were clinically free from symptoms and Wassermann negative; 14.8 percent had no clinical symptoms with Wassermann positive; 14.1 percent had heart and vessel disease; 2.76 percent had general paresis and 1.27 percent had tabes dorsalis. Thus in 1932, as the Public Health Service put forth a major effort toward control and treatment, much was still unknown regarding the latent stages of the disease especially pertaining to its natural course and the epidemiology of late and latent syphilis.

Facts and Documentation Pertaining to Charge I-A

1. There is no protocol which documents the original intent of the study. None of the literature searches or interviews with participants in the study gave any evidence that a written protocol ever existed for this study. The theories postulated from time to time include the following purposes either by direct statement or implication:[5-7]

   a. Study of the natural history of the disease.

   b. Study of the course of treated and untreated syphilis (Annual Report of the Surgeon General of the Public Health Service of the United States 1935-36).

   c. Study of the differences in histological and clinical course of the disease in black versus white subjects.

   d. Study with an "acceptance" of the postulate that there was a benign course of the disease in later stages vis-a-vis the dangers of available therapy.

   e. Short term study (6 months or longer) of the incidence and clinical course of late latent syphilis in the Negro male (From letter of correspondence from T. Clark, Assistant Surgeon General, to M.M. Davis of the Rosenwald Fund, October 29, 1932) – Original plan of procedure is stated herein.

   f. A study which would provide valuable data for a syphilis control program for a rural impoverished community.

In the absence of an original protocol, it can only be assumed that between 1932 and 1936 (when the first report[5] of the study was made) the decision was made to continue the study as a long-term study. The Annual Report of the Surgeon General for 1935-36 included the statement: "Plans for the continuation of this study are underway. During the last 12 months, success has been obtained in gaining permission for the performance of autopsies on 11/15 individuals who died."

2. There is no evidence that informed consent was gained from the human participants in this study. Such consent would and should have included knowledge of the risk of human life for the involved parties and

information re possible infections of innocent, non-participating parties such as friends and relatives. Reports such as "Only individuals giving a history of infection who submitted voluntarily to examination were included in the 399 cases" are the only ones that are documentable.[5] Submitting voluntarily is not informed consent.

3. In 1932, there was a known risk to human life and transmission of the disease in latent and late syphilis* was believed to be possible. Moore[3] 1932 reported satisfactory clinical outcome in 85% of patients with latent syphilis that were treated in contrast to 35% if no treatment is given.

4. The study as announced and continually described as involving "untreated" male Negro subjects was not a study of "untreated" subjects. Caldwell[8] in 1971 reported that: All but one of the originally untreated syphilitics seen in 1968-1970 have received therapy, although heavy metals and/or antibiotics were given for a variety of reasons by many non-study physicians and not necessarily in doses considered curative for syphilis. Heller[6] in 1946 reported "about one-fourth of the syphilitic individuals received treatment for their infection. Most of these, however, received no more than 1 or 2 arsenical injections; only 12 received as many as 10." The "untreated" group in this study is therefore a group of treated *and* untreated male subjects.

5. There is evidence that control subjects who became syphilitic were transferred to the "untreated" group. This data is present in the patient files at the Center for Disease Control in Atlanta. Caldwell[8] reports 12 original controls either acquired syphilis or were found to have reactive treponemal tests (unavailable prior to 1953). Heller,[6] also, reported that "It is known that some of the control group have acquired syphilis although the exact number cannot be accurately determined at present." Since this transfer of patients from the control group to the syphilitic group did occur, the study is not one of late latent syphilis. Also, it is not certain that this group of patients did in fact receive adequate therapy.

6. In the absence of a definitive protocol, there is no evidence or assurance that standardization of evaluative procedures, which are essential to the validity and reliability of a scientific study, existed at any time. This fact leaves open to question the true scientific merits of a longitudinal study of this nature. Standardization of evaluative procedures and clinical judgment of the investigators are considered essential to the valid interpretation of clinical data.[9] It should be noted that, in 1932, orderly and well planned research related to latent syphilis was justifiable since a. Morbidity and mortality had not been documented for this population and the significance of the survey procedure had just been reported in findings of the prevalence studies for 6 southern counties;[1] b. Epidemiologic knowledge of syphilis at the time had not produced facts so that it could be scientifically documented "just how and at what stage the disease is spread."* c. There was a paucity of knowledge re clinical aspects and spontaneous cure in latent syphilis[3] and the Oslo study[4] had just reported spontaneous remission of the disease in 27.7% of the patients studied. If perhaps a higher "cure" rate could have been documented for the latent syphilitics, then the treatment priorities and recommendations may have been altered for this community where funds and medical services were already inadequate.

The retrospective summary of the "Scientific Contributions of the Tuskegee Study" from the Chief, Venereal Disease Branch, USPHS (dated November 21, 1972) includes the following merits of the study:

> "Knowledge already gained or potentially able to be gained from this study may be categorized as contributing to improvements in the following areas:
>
> 1. Care of the surviving participants,
> 2. Care of all persons with latent syphilis,
> 3. The operation of a national syphilis control program,
> 4. Understanding of the disease of syphilis,
> 5. Understanding of basic disease producing mechanisms."

Panel Judgments on Charge 1-A

1. In retrospect, the Public Health Service Study of Untreated Syphilis in the Male Negro in Macon County, Alabama, was ethically unjustified in 1932. This judgment made in 1973 about the conduct of the study in 1932 is made with the advantage of hindsight acutely sharpened over some forty years, concerning an activity in a different age with different social standards. Nevertheless one fundamental ethical rule is that a person should not be subjected to avoidable risk of death or physical harm unless he freely and intelligently consents. There is no evidence that such consent was obtained from the participants in this study.

2. Because of the paucity of information available today on the manner in which the study was conceived, designed and sustained, a scientific justification for a short term demonstration study cannot be ruled out. However, the conduct of the longitudinal study as initially reported in 1936 and through the years is

*Vonderlehr to T. Clark — Memorandum — June 10, 1932.

*Letter from L. Usilton, VD Program 1930-32 and memorandum from Vonderlehr to T. Clark (Assistant Surgeon General) June 10, 1932.

judged to be scientifically unsound and its results are disproportionately meager compared with known risks to human subjects involved. Outstanding weaknesses of this study, supported by the lack of written protocol, include lack of validity and reliability assurances; lack of calibration of investigator responses; uncertain quality of clinical judgments between various investigators; questionable data base validity and questionable value of the experimental design for a long term study of this nature.

The position of the Panel must not be construed to be a general repudiation of scientific research with human subjects. It is possible that a scientific study in 1932 of untreated syphilis, properly conceived with a clear protocol and conducted with suitable subjects who fully understood the implications of their involvement, might have been justified in the pre-penicillin era. This is especially true when one considers the uncertain nature of the results of treatment of late latent syphilis and the highly toxic nature of therapeutic agents then available.

REPORT ON CHARGE I-B

Statement of Charge I-B: Determine whether the study should have been continued when penicillin became generally available.

Background Data

In 1932, treatment of syphilis in all stages was being provided through the use of a variety of chemotherapeutic agents including mercury, bismuth, arsphenamine, neoarsphenamine, iodides and various combinations thereof. Treatment procedures being used in the early 1930's extended over long periods of time (up to two years) and were not without hazard to the patient.[10] As of 1932, also, treatment was widely recommended and treatment schedules specifically for late latent syphilis were published and in use.[3 10] The rationale for treatment at that time was based on the clinical judgment "that the latent syphilitic patient must be regarded as a potential carrier of the disease and should be treated for the sake of the Community's health."[3] The aims of treatment in the treatment of latent syphilis were stated to be: 1) to increase the probability of "cure" or arrest, 2) to decrease the probability of progression or relapse over the probable result if no treatment were given and 3) the control of potential infectiousness from contact of the patient with adults of either sex, or in the case of women with latent syphilis, for unborn children.

According to Pfeiffer (1935),[11] treatment of late syphilis is quite individualistic and requires the physician's best judgment based upon sound fundamental knowledge of internal medicine and experience, and should not be undertaken as a routine procedure. Thus, treatment was being recommended in the United States for all stages of syphilis as of 1932 despite the "spontaneous" cure concept that was being justified by interpretations of the Oslo study, the potential hazards of treatment due to drug toxicity and to possible Jarisch-Herxheimer reactions in acute late syphilis.[12]

Documented reports of the effects of penicillin in the 1940's and early 1950's vary from outright support and endorsement of the use of penicillin in late and latent syphilis,[13-15] to statements of possible little or no value,[16-17] to expressions of doubts and uncertainty[18-19] related to its value, the potency of penicillin, absence of control of the rate of absorption, and potential hazard related to severe Herxheimer effects.

Although the mechanism of action of penicillin is not clear from available scientific reports of late latent syphilis, the therapeutic benefits were clinically documented by the early 1950's and have been widely reported from the mid 1950's to the present. In fact, the Center for Disease Control of the USPHS has reported treatment of syphilitic mothers in all stages of infection with penicillin as of 1953[20] and has demonstrated that penicillin is the most effective treatment yet known for neurosyphilis (1960).[21]

Facts and Documentation re Charge I-B

1. Treatment schedules recommending the use of arsenicals and bismuth in the treatment of late latent syphilis were available in 1932.[3] Penicillin therapy was recommended for treatment of late latent syphilis in the late 1940's[14-15] which was *before* it became readily available for public use (estimated to have been 1952-53).

2. It was "known as early as 1932 that 85% of patients treated in late latent syphilis would enjoy prolonged maintenance of good health and freedom from disease as opposed to 35 percent if left untreated."[3] Scientists in this study,[5] reported in 1936, that morbidity in male Negroes with untreated syphilis far exceeds that in a comparable nonsyphilitic group and that cardiovascular and central nervous system involvements were two to three times as common. Moreover, Wenger,[22] in 1950, reported: "We know now, where we could only surmise before, that we have contributed to their ailments and shortened their lives. I think the least we can say is that we have a high moral obligation to those that have died to make this the best study possible." The effect of syphilis in shortening life was published from observations made by Usilton et al. in 1937.[23] The study by Rosahn[24] at Yale in 1947 reported strong clinical evidence that syphilis ran a more fatal course in Negroes than in Caucasians.

3. Reports regarding the withholding of treatment from patients in this study are varied and are still subject to controversy. Statements received from personal interviews conducted by Panel members with participants in this study cannot be considered as conclusive since there are varied opinions concerning what actually happened. In written letters and in open interviews, the panel received reports that treatment was deliberately withheld on the one hand and on the other, we were told that individuals seeking treatment were not denied treatment (in transcript and correspondence documents).

What is clearly documentable (in a series of letters between Vonderlehr and Health officials in Tuskegee taking place between February 1941 and August 1942) is that known seropositive, untreated males under 45 years of age from the Tuskegee Study had been called for army duty and rejected on account of a positive blood. The local board was furnished with a list of 256

names of men under 45 years of age and asked that these men be excluded from the list of draftees needing treatment! According to the letters, the board agreed with this arrangement in order to make it possible to continue this study on an effective basis. It should be noted that some of these patients had already received notices from the Local Selective Service Board "to begin their antisyphilitic treatment immediately."

According to Wenger,[22] the patients in the study "received no treatment on our recommendation." At the present time, we know that most of the participants in this study received some form of treatment with heavy metals and/or antibiotics.[8] Although the adequacy of treatment received is not known, it is clear that the treatment received was provided by physicians who were not a part of the study and who were individually sought by the individual patients related to their own medical symptoms and pursuit of treatment.

4. The five survey periods in this study occurred in 1932, 1938-39, 1948, 1952-53 and 1968-70.[8-25] This study lacks continuity except through the public health nurse and at these isolated survey periods. In 1969 an Ad Hoc Committee reviewed the Tuskegee Study with the purpose: to examine data from the Tuskegee Study and offer advice on continuance of this study.

Participants of the February 6, 1969 meeting included:

Committee Members:

Dr. Gene Stollerman
Chairman, Dept. of Medicine
University of Tennessee, Memphis

Dr. Johannes Ipsen, Jr.
Professor
Dept. of Community Medicine
University of Pennsylvania, Philadelphia

Dr. Ira Myers
State Health Officer
Montgomery

Dr. J. Lawton Smith
Associate Professor of Ophthalmology
University of Miami

Dr. Clyde Kaiser
Senior Member Technical Staff
Milbank Memorial Fund
New York City

Resource Persons:

Dr. Bobby C. Brown, VDRL, NCDC
Mrs. Eleanor V. Price, VD Branch, NCDC
Dr. Joseph Caldwell, VD Branch, NCDC
Dr. Paul Cohen, VDRL, NCDC

Dr. Sidney Olansky
Professor of Medicine
Dept. of Internal Medicine
Emory University Clinic, Atlanta

Recorders:

Dr. Leslie C. Norins
Chief, VDRL, NCDC

Mrs. Doris J. Smith
Secretary to Dr. Norins, VDRL, NCDC

Attending:

Dr. David J. Sencer
Director, NCDC

Dr. William J. Brown
Chief, VD Branch, NCDC

Dr. U.S.G. Kuhn, III, VDRL, NCDC

Miss Genevieve W. Stout, VDRL, NCDC

Dr. H. Bruce Dull
Assistant Director, NCDC

The meeting was convened at 1:00 p.m. and adjourned at 4:10 p.m.

A summary report of the meeting includes the following:

The purpose of the meeting was to determine if the Tuskegee Study should be terminated or continued.

Considerations were:

1. How the study was setup in 1932
2. Are the participants all available
3. How are the survivors faring

At the time of this study there were only seven patients whose primary cause of death was ascribed to syphilis.

It was determined that benefits to be achieved from the study at this time were:

1. Relationship of serology to morbidity from syphilis
2. Relationship of known pathology to syphilis
3. Various epidemiological considerations

Full treatment of the survivors was also considered and the following liabilities listed.

Danger of late Herxheimer's reaction which would worsen or possibly kill those syphilitic patients suffering from cardiovascular or neurological conditions.

At this time it was mentioned that both Macon County Health Department and Tuskegee Institute were cognizant of the study.

The meeting was terminated with several salient points.

1. This type of study would never be repeated.
2. There were certain medical facts to be learned by continuing the present study.
3. Treatment for these patients was not indicated unless they had signs of active syphilitic disease.
4. More contact should be established between PHS and Macon County Health Department and Medical Society so they would cooperate in the continuance of the study.

It should be noted that the Committee was eminently represented from the medical community. However, legal representatives and others from the non-medical community of scholars were not adequately represented for so sensitive a study. This is especially true since the Tuskegee Study was being continued at a time when Department of Health, Education, and Welfare guidelines for the Protection of Human Subjects were being widely disseminated for compliance by all institutions receiving grant support. The three hours and ten minutes were not adequate for in-depth study of the broad issues, implications and ramifications of this study.

In 1970, Drs. Anne Yobs and Arnold L. Schroeter in separate memoranda (to the Director, Center for Disease Control and to the Chief, Venereal Disease Branch) recommended procedures for orderly termination of this study. Dr. James Lucas, Assistant Chief of the Venereal Disease Branch, in a memorandum to the Chief of the Venereal Disease Branch dated September 10, 1970 states: It must be fully realized that the remaining contribution from this study will be largely of *historical* interest. Nothing learned will prevent, find, or cure a single case of infectious syphilis or bring us closer to our basic mission of controlling venereal disease in the United States.

5. There is a crucial absence of evidence that patients were given a "choice" of continuing in the study once penicillin became readily available. This fact serves to amplify the magnitude of encroachment on the human lives and well-being of the participants in this study. This is especially significant when there is uncertainty as to the whole issue of "consent" of the participants.

Panel Judgments on Charge I-B

The ethical, legal and scientific implications which are evoked from the facts presented in the previous section led the Panel to the following judgment:

That penicillin therapy should have been made available to the participants in this study especially as of 1953 when penicillin became generally available.

Withholding of penicillin, after it became generally available, amplified the injustice to which this group of human beings had already been subjected. The scientific merits of the Tuskegee Study are vastly overshadowed by the violation of basic ethical principles pertaining to human dignity and human life imposed on the experimental subjects.

REPORT ON CHARGE I

SUMMARY

This section of the Advisory Panel's report deals specifically with Charge Codes I-A and I-B.

Statement of Charge Codes

Charge I-A. Determine whether the study was justified in 1932, and

Charge I-B. Determine whether it should have been continued when penicillin became generally available.

Introduction

The Background Paper on the Tuskegee Study, prepared by the Venereal Disease Branch of the Center for Disease Control, July 27, 1972, included the following statements:

"Because of the lack of knowledge of the pathogenesis of syphilis, a long-term study of untreated syphilis was considered desirable in establishing a more knowledgeable syphilis control program."

"A prospective study was begun late in 1932 in Macon County, Alabama, a rural area with a static population and a high rate of untreated syphilis. An untreated population such as this offered an unusual opportunity to follow and study the disease over a long period of time. In 1932, a total of 26 percent of the male population tested, who were 25 years of age or older, were serologically reactive for syphilis by at least two tests, usually on two occasions. The original study group was composed of 399 of these men who had received no therapy and who gave historical and laboratory evidence of syphilis which had progressed beyond the infectious stages. A total of 201 men comparable in age and environment and judged by serology, history, and physical examination to be free of syphilis were selected to be the control group."

Panel Conclusions re Charge I-A and I-B of the Tuskegee Study

After extensive review of the available documents, interviews with associated parties and pursuit of various other avenues of documentation, the Panel concludes that:

1. In retrospect, the Public Health Service Study of Untreated Syphilis in the Male Negro in Macon County, Alabama was ethically unjustified in 1932.

2. Because of the paucity of information available today on the manner in which the study was conceived, designed and sustained, scientific justification for a short-term demonstration study in 1932 cannot be ruled out. However, the conduct of the longitudinal study as initially reported in 1936 and through the years is judged to be scientifically unsound and its results are disproportionately meager compared with known risks to the human subjects involved.

3. Penicillin therapy should have been made available to the participants in this study not later than 1953.

The Panel qualifies its conclusions with several position statements summarized as follows:

a. The judgments in 1973 about the conduct of the Tuskegee Study in 1932 are made with the advantage of hindsight, acutely sharpened over some forty years concerning an activity in a different age with different social standards. Nevertheless one fundamental ethical rule is that a person should not be subjected to avoidable risk of death or physical harm unless he freely and intelligently consents. There was no evidence that such consent was obtained from the participants in this study.

b. History has shown that certain people under psychological, social or economic duress are particularly acquiescent. These are the young, the mentally impaired, the institutionalized, the poor and persons of racial minority and other disadvantaged groups. These are the people who may be selected for human experimentation and who, because of their station in life, may not have an equal chance to withhold consent.

c. The Tuskegee Syphilis Study, placed in the perspective of its early years, is not an isolated event in terms of the generally accepted conditions and practices that prevailed in the 1930's.

d. The position of the Panel must not be construed to be a general repudiation of scientific research with human subjects. It is possible that a scientific study in 1932 of untreated syphilis, properly conceived with a clear protocol and conducted with suitable subjects who fully understood the implications of their involvement, might have been justified in the pre-penicillin era because of the uncertain nature of results of treatment of late latent syphilis with the highly toxic therapeutic agents then available.

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Respectfully Submitted,

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Approval with Reservations:
(See addendum for reservation statement)
Jay Katz, M.D.
Vernal Cave, M.D.

Abstention:
Broadus N. Butler, Ph.D.

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TO: THE ASSISTANT SECRETARY FOR HEALTH AND SCIENTIFIC AFFAIRS

FROM: JAY KATZ, M.D.

TOPIC: RESERVATIONS ABOUT THE PANEL REPORT ON CHARGE I

I should like to add the following findings and observations to the majority opinion:

(1) There is ample evidence in the records available to us that the consent to participation was not obtained from the Tuskegee Syphilis Study subjects, but that instead they were exploited, manipulated, and deceived. They were treated not as human subjects but as objects of research. The most fundamental reason for condemning the Tuskegee Study at its inception and throughout its continuation is not that all the subjects should have been treated, for some might not have wished to be treated, but rather that they were never fairly consulted about the research project, its consequences for them, and the alternatives available to them. Those who for reasons of intellectual incapacity could not have been so consulted should not have been invited to participate in the study in the first place.

(2) It was already known before the Tuskegee Syphilis Study was begun, and reconfirmed by the study itself, that persons with untreated syphilis have a higher death rate than those who have been treated. The life expectancy of at least forty subjects in the study was markedly decreased for lack of treatment.

(3) In addition, the untreated and the "inadvertently" (using the word frequently employed by the investigators) but inadequately treated subjects suffered many complications which could have been ameliorated with treatment. This fact was noted on occasion in the published reports of the Tuskegee Syphilis Study and as late as 1971. However the subjects were not apprised of this possibility.

(4) One of the senior investigators wrote in 1936 that since "a considerable portion of the infected Negro population remained untreated during the entire course of syphilis. . .an unusual opportunity (arose) to study the untreated syphilitic patient from the beginning of the disease to the death of the infected person." Throughout, the investigators seem to have confused the study with an "experiment in nature." But syphilis was not a condition for which no beneficial treatment was available, calling for experimentation to learn more about the condition in the hope of finding a remedy. The persistence of the syphilitic disease from which the victims of the Tuskegee Study suffered resulted from the unwillingness or incapacity of society to mobilize the necessary resources for treatment. The investigators, the USPHS, and the private foundations who gave support to this study should not have exploited this situation in the fashion they did. Unless they could have guaranteed knowledgeable participation by the subjects, they all should have disappeared from the research scene or else utilized their limited research resources for therapeutic ends. Instead, the investigators believed that the persons involved in the Tuskegee Study would *never* seek out treatment; a completely unwarranted assumption which ultimately led the investigators deliberately to obstruct the opportunity for treatment of a number of the participants.

(5) In theory if not in practice, it has long been "a principle of medical and surgical morality (never to perform) on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science" (Claude Bernard 1865), at least without the knowledgeable consent of the subject. This was one basis on which the German physicians who had conducted medical experiments in concentration camps were tried by the Nuremberg Military Tribunal for crimes against humanity. Testimony at their trial by official representatives of the American Medical Association clearly suggested that research like the Tuskegee Syphilis Study would have been intolerable in this country or anywhere in the civilized world. Yet the Tuskegee study was continued after the Nuremberg findings and the Nuremberg Code had been widely disseminated to the medical community. Moreover, the study was not reviewed in 1966 after the Surgeon General of the USPHS promulgated his guidelines for the ethical conduct of research, even though this study was carried on within the purview of his department.

(6) The Tuskegee Syphilis Study finally was reviewed in 1969. A lengthier transcript of the proceedings, not quoted by the majority, reveals that one of the five members of the reviewing committee repeatedly emphasized that a moral obligation existed to provide treatment for the "patients." His plea remained unheeded. Instead the Committee, which was in part concerned with the possibility of adverse criticism, seemed to be reassured by the observation that "if we established good liaison with the local medical society, there would be no need to answer criticism."

(7) The controversy over the effectiveness and the dangers of arsenic and heavy metal treatment in 1932 and of penicillin treatment when it was introduced as a method of therapy is beside the point. For the real issue is that the participants in this study were never informed of the availability of treatment because the

investigators were never in favor of such treatment. Throughout the study the responsibility rested heavily on the shoulders of the investigators to make every effort to apprise the subjects of what could be done for them if they so wished. In 1937 the then Surgeon General of the USPHS wrote: "(f) or late syphilis no blanket prescription can be written. Each patient is a law unto himself. For every syphilis patient, late and early, a careful physical examination is necessary before starting treatment and should be repeated frequently during its course." Even prior to that, in 1932, ranking USPHS physicians stated in a series of articles that adequate treatment "will afford a practical, if not complete guaranty of freedom from the development of any late lesions. . ."

In conclusion, I note sadly that the medical profession, through its national association, its many individual societies, and its journals, has on the whole not reacted to this study except by ignoring it. One lengthy editorial appeared in the October 1972 issue of the Southern Medical Journal which exonerated the study and chastised the "irresponsible press" for bringing it to public attention. When will we take seriously our responsibilities, particularly to the disadvantaged in our midst who so consistently throughout history have been the first to be selected for human research?

Respectfully submitted,

(sgd.) Jay Katz, M.D.

REPORT ON CHARGE II

Transmittal Note from Chairman of Subcommittee on Charge II

This report on Charge II was prepared by the Subcommittee on Charge II (Ronald H. Brown, J.D., Jean L. Harris, M.D., F.R.S.H., Jay Katz, M.D., F.A.C.P., Fred Speaker, J.D., Jeanne C. Sinkford, D.D.S., Ph.D., Secretary, Vernal G. Cave, M.D., F.A.C.P., Chairman).

The provisional basis for this report which was the result of the earliest deliberations the panel dealt with is now amply substantiated by our documentations, conclusions, and recommendations under Charges I and III. On behalf of the entire subcommittee, the Chairman expresses deep thanks and appreciation for their splended cooperation to Dr. Robert C. Backus, Mr. Robert Rawles, Mr. James Morant, Mrs. Jacqueline Eagle, and Mrs. Bernice M. Lee.

LETTER OF TRANSMISSION

October 27, 1972

Merlin K. DuVal, M.D.
Assistant Secretary for
Health and Scientific Affairs
Department of Health, Education,
and Welfare
Washington, D.C. 20201

Dear Dr. DuVal:

As Chairman of the Tuskegee Syphilis Study Ad Hoc Advisory Panel, I enclose our first report to you, relating only to the second charge of the three assigned to the Panel. Although one member of the Panel was in hospital on the day this report was put into form for transmission to you, her written suggestions concerning an earlier draft have been incorporated. Hence, the report represents concurrence of the Panel as a whole.

You will note that our initial recommendations call for some very early steps on your part. We as a Panel, along with the excellent staff that is assisting our work, stand ready to help you to implement the recommendations in any way.

It is our understanding, on the basis of the statements you made to us at our orientation meeting, that our reports to you, including this initial one, will be made public only by you whether or not you decide to accept and implement our recommendations.

Since agreeing on the enclosed report, two-thirds of our Panel have been able to engage in a first-hand investigation for two days, in Macon County, Alabama. Nothing that we have discovered through this recent field visit has afforded us cause to alter any part of the enclosed report concerning the second charge. The first-hand investigation, brief as it has been, has provided us with information and new understandings that will prove of great value in our subsequent work on charges 1 and 3.

Sincerely,

(sgd.) Broadus N. Butler, Ph.D.
Chairman
Tuskegee Syphilis Study
Ad Hoc Advisory Panel

October 25, 1972

INITIAL RECOMMENDATION OF THE TUSKEGEE SYPHILIS STUDY AD HOC ADVISORY PANEL

The Charter of the Tuskegee Syphilis Study Ad Hoc Advisory Panel, issued on August 28, 1972, mandates advice on three specific aspects of the study of untreated syphilis initiated by the Public Health Service in 1932. Item two of the three charges requires the Panel to:

> "Recommend whether the study should be continued at this point in time, and if not, how it should be terminated in a way consistent with the rights and health needs of its remaining participants."

Initially, the Panel has limited its deliberations and recommendations exclusively to this charge, and the recommendations contained in this report are intended to respond solely to this specific issue.

In determining our initial recommendations, the Panel has made inquiries which have led us to accept certain evidence outlined here. Though our research on the background and conduct of the Tuskegee Syphilis Study has not been completed, the Panel is satisfied that in the light of its preliminary findings, which will be fully documented at a later date, the recommendations set forth below are fully justified.

BACKGROUND

Since 1932, under the leadership, direction and guidance of the United States Public Health Service, there has been a continuing study, centered in Macon County, Alabama, of the effect of untreated syphilitic infection in approximately 400 Black male human beings previously infected with syphilis as subjects. In the pursuit of this study approximately 200 Black male human beings without syphilis were followed as controls. No convincing evidence has been presented to this Panel that participants in this study were adequately informed about the nature of the experiment, either at its inception or subsequently.

The United States Public Health Service from the onset of the study has maintained a continuous policy of withholding treatment for syphilis from the infected subjects. There was common medical knowledge, before this study, that untreated syphilitic infection produces disability and premature mortality. To date, including its earliest reports, this study has confirmed that untreated syphilitic infection produces disability and premature mortality. Since the late 1940's numerous medical authorities have recommended treatment for syphilis with penicillin in all stages of the disease, including late latent syphilis and tertiary syphilis.

A technical and medical advisory panel convened in 1969 by the United States Public Health Service is reported to have recommended with some ambiguity, that the participants surviving at that time should not be treated. It is estimated that approximately 125 of the participants, including 50 of the controls, are still alive; and the current health status of the participants in the Tuskegee Study is not known.

RECOMMENDATIONS

I. Termination:

The study of *untreated* syphilis in Black males in Macon County, Alabama, now known as the "Tuskegee Syphilis Study," should be terminated immediately. With this most basic recommendation, the participants involved in this study are to be given the care now required to treat any disabilities resulting from their participation. In furtherance of this goal we recommend:

A. That Select Specialists Group, composed of competent doctors and other appropriate persons, with experience in the problems arising from this study, be appointed by the Assistant Secretary for Health and Scientific Affairs, DHEW, no later than fifteen days after the adoption of these recommendations.

B. That the members of the Select Specialists Group have had no prior involvement in the Tuskegee Syphilis Study.

C. That the Select Specialists Group be composed of, but not necessarily be limited to, a dermatologist with experience in syphilology who will serve as Chairman, two internists (at least one of whom shall be a cardiologist), a radiologist, a neurologist, an ophthalmologist, a psychiatrist, a doctor of dental surgery, and a social worker.

D. That the Select Specialists Group be solely charged to apply its expert diagnostic and therapeutic skills in order to safeguard the best interests of the participants and of others who may have been infected as a result of the withholding of treatment from the participants.

E. That the Select Specialists Group be vested with the full legally permissible medical authority, medical supervision and medical judgment with regard to the treatment or referral of all of the surviving participants and others within and outside Macon County who may be identified, in cooperation with the

appropriate medical societies and Health Departments.

F. That the Public Health Service immediately inform all surviving participants of the nature of their participation in the study, and the desire of the Public Health Service to assess their current health status.

G. That the members of the "Subcommittee on Medical Care" of the Tuskegee Syphilis Study Ad Hoc Advisory Panel be ex-officio members of the Select Specialists Group to function primarily as liaison between the Select Specialists Group and the entire Panel.

H. That on completion of its charge, the Select Specialists Group submit a detailed report about its activities to the Tuskegee Syphilis Study Ad Hoc Advisory Panel through its Chairman. This report shall include, but by no means be limited to, the reasons for administering or withholding penicillin and other drug treatment for syphilis from untreated participants who are infected with syphilis.

I. That the highest priorities be given to this mission so that the charge to the Select Specialists Group shall be completed at the earliest possible date consistent with the best interests of the participants and the ethical responsibilities of the Department of Health, Education, and Welfare.

II. Assessment, Treatment and Care

A. That arrangements be made with *all speed* for the immediate health assessment, treatment and care of all persons included in the study in a suitably adequate facility easily accessible to the surviving participants. That whenever a participant expresses the wish to be cared for or treated by physicians of his own choice, such choices be respected and given all necessary support.

B. That every effort be made to preserve confidentiality with respect to the identification of any participant.

C. That the United States Public Health Service's epidemiologists be mobilized, on a highest priority basis, to assist in locating all surviving participants as well as others who may have been infected as a result of the withholding of treatment from the participants.

III. Encouragement of Participation:

A. That adequate arrangements be provided for maintaining present standards of living during the evaluation and treatment periods in order to minimize any economic barriers to the cooperation of the participants.

B. That at a minimum, any benefits which have been promised to the participants in the past continue to remain in effect.

Respectfully submitted,

Broadus N. Butler, Ph.D.
Ronald H. Brown
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Fred Speaker
Barney H. Weeks

October 27, 1972

TO: ASSISTANT SECRETARY FOR HEALTH AND SCIENTIFIC AFFAIRS

FROM: JAY KATZ, M.D.

SUBJECT: ADDENDUM TO PANEL REPORT ON CHARGE II

I entirely concur in the Panel's recommendations and in the reasons given therefor. However, one additional piece of evidence lends even greater conviction, if any is still needed, to the decision to terminate the Tuskegee Syphilis Study. We have been informed that no scientific knowledge of any consequence would be derived from its continuation. The Panel felt that recording this fact might create the impression that it was *the* major reason for terminating the study. I believe that its inclusion should not, and would not, be so construed.

There are cogent reasons for not dismissing the issue of scientific merit. As long as society continues to favor the pursuit of medical knowledge for the possible benefit of the patients participating in research or for the benefit of future patients, a balancing of risks and benefits is inevitable. We must acknowledge this reality in order to confront such questions as: Do we wish to preserve this balancing process and, if we do, how might we learn to minimize inevitable harm to subjects and science? We urgently need to establish an orderly process which will permit the assessment of the conflicting claims inherent in decisions to initiate, continue or terminate research projects. Such an assessment might proceed in four steps: (1) a relentless inquiry into the harmful consequences to the participants; (2) an appraisal of the benefits which may accrue to science as well as to society: (3) a balancing of the risks to the participants against the benefits to them and/or science; and (4) an anticipatory rebuttal to the charge that either the interests of the participants or of science have not been sufficiently considered. In the light of the finding that no interests of science are surrendered by terminating the Tuskegee Syphilis Study, there is nothing to balance and nothing to rebut, and continuance of the study would for this reason alone be inadmissible.

I appreciate that had the conclusion been otherwise, the study would in all probability still have to be terminated because of the other findings set forth in the Panel's report, findings which will be further explored in our deliberations with respect to Charge One ("whether the study was justified"). Moreover, I should note that the four factors, listed above, do not directly address themselves to such other important considerations as: who should be selected for research, what disclosures must be made to participants in research, etc. This will surely be considered in our response to Charge Three ("whether existing (research) policies are adequate and effective"). Finally, I also leave unconsidered for now another question which emerges from the finding of "no scientific merit": why was the study not terminated at a time prior to the appointment of this Panel? One of the benefits of including a finding of scientific merit in every assessment is that many more projects might be terminated sooner, because the reviewer would be hard pressed to make an affirmative finding on this issue.

Respectfully submitted,

(sgd.) Jay Katz, M.D.

REPORT ON CHARGE III

TO: THE ASSISTANT SECRETARY FOR HEALTH

FROM: TUSKEGEE SYPHILIS STUDY AD HOC ADVISORY PANEL

TOPIC: FINAL REPORT ON CHARGE III

I. INTRODUCTION

In his third charge to the Tuskegee Syphilis Study Ad Hoc Advisory Panel, Dr. Merlin K. DuVal, the HEW Assistant Secretary for Health and Scientific Affairs, has asked us to determine

> whether existing policies to protect the rights of patients participating in health research conducted or supported by the Department of Health, Education, and Welfare are adequate and effective and to recommend improvements in these policies, if needed.

Our response to this charge, embodied in this report, should not be viewed simply as a reaction to a single ethically objectionable research project. For the Tuskegee Syphilis Study, despite its widespread publicity was not an isolated phenomenon. We believe that the revelations from Macon County merely brought to the surface once again the unresolved problems which have long plagued medical research activities. Indeed, we hasten to add that although we refer in this report almost exclusively to physicians and to biomedical investigations, the issues we explore also arise in the context of non-medical investigations with human beings, conducted by psychologists, sociologists, educators, lawyers and others. The scope of the DHEW Policy on Protection of Human Subjects, broadened in 1971 to encompass such research, attests to the increasing significance of non-medical investigations with human beings.

Our initial determination that the protection of human research subjects is a current and widespread problem should not be surprising, especially in light of the recent Congressional hearings and bills focusing on the regulation of experimentation. In the past decade the press has publicized and debated a number of experiments which raised ethical questions: for example, the injection of cancer cells into aged patients at the Jewish Chronic Disease Hospital in Brooklyn, the deliberate infection of mentally retarded children with hepatitis at Willowbrook, the development of heart transplantation techniques, the enormous amount of drug research conducted in American prisons, the whole-body irradiation treatment of cancer patients at the University of Cincinnati, the advent and spread of "psychosurgery," and the Tuskegee Syphilis Study itself.

With so many dramatic projects coming to the attention of the general public, more must lie beneath the surface. Evidence for this too has been forthcoming. In 1966, Dr. Henry K. Beecher, the eminent Dorr Professor of Research in Anesthesia at the Harvard Medical School, charged in the prestigious New England Journal of Medicine that "many of the patients (used in experiments which Dr. Beecher investigated and reported) never had the risk satisfactorily explained to them, and. . .further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered as the direct result. . ."[1] Dr. Beecher concluded that "unethical or questionably ethical procedures are not uncommon."[2] Quite recently this charge has been corroborated by the sociologist Bernard Barber and his associates, who interviewed biomedical researchers about their own research practices.[3] Despite the expected tendency of researchers to minimize ethical problems in their own work, Barber *et al.* were able to conclude that "while the large majority of our samples of biomedical researchers seems to hold and live up to high ethical standards, a significant minority may not."[4]

The problem of ethical experimentation is the product of the unresolved conflict between two strongly held values: the dignity and integrity of the individual, and the freedom of scientific inquiry. Professionals of many disciplines, and researchers especially, exercise unexamined discretion to intervene in the lives of their subjects for the sake of scientific progress. Although exposure to needless harm and neglect of the duty to obtain the subject's consent have generally been frowned upon in theory, the infliction of unnecessary harm and infringements on informed consent are frequently accepted, in practice, as the price to be paid for the advancement of knowledge. How have investigators come to claim this sweeping prerogative? If the answer to this question is that "society" has authorized professionals to choose between scientific progress and

*This report was prepared by the Subcommittee on Charge III (Jay Katz, M.D., chairman, Ronald H. Brown, J.D., Seward Hiltner, Ph.D. and Fred Speaker, J.D.). The subcommittee chairman wishes to thank his research assistant Stephen H. Glickman, a third year law student at Yale University, for his valuable contributions to this report. Special thanks go also to Dr. Robert C. Backus, Mrs. Bernice M. Lee and Ms. Jackie Eagle who in many ways facilitated the work of the subcommittee.

1. Beecher, "Ethics and Clinical Research," 274 New Eng. J. Med. 1354 (1966)
2. *Ibid.*, p. 1355.
3. Barber, Lally, Makarushka, and Sullivan, *Research on Human Subjects: Problems of Social Control in Medical Experimentation* (Russell Sage Foundation 1973) (hereinafter, *Barber et al.)*
4. *Barber et al., supra,* footnote 3, at 52.

individual human dignity and welfare, should not "society" retain some control over the research enterprise? We agree with philosopher Hans Jonas that

> a slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.[5]

We have, as will be seen, made far-reaching recommendations for change. We do not propose these changes lightly. But throughout, in accordance with our mandate, our concern has not been just to define the ethical issues, but also to examine the structures and policies thus far devised to deal with those issues. In urging greater societal involvement in the research enterprise, we believe that the goal of scientific progress can be harmonized with the need to assure the protection of human subjects.

5. Jonas, "Philosophical Reflections on Experimenting with Human Subjects," 98 *Daedalus* 219, 245 (1969).

II. SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

A. Evaluation of Current DHEW Policies for the Protection of Human Research Subjects

1. No uniform Departmental policy for the protection of research subjects exists. Instead one policy governs "extramural" research – research supported by DHEW grants or contracts to institutions outside the Federal Government and conducted by private researchers – and another policy governs "intramural" research – research conducted by personnel of the Public Health Service. Furthermore. Food and Drug Administration (FDA) regulations promulgated to protect subjects in drug research, whether or not supported by DHEW or conducted by the PHS, incorporate variations of their own. The lack of uniformity in DHEW policies creates confusion, and denies some subjects the protection they deserve.

Moving to the next higher level, no uniform Federal policies exist for the protection of subjects in Government-sponsored research. Other agencies wholly separate from DHEW – most notably, the Department of Defense – support or conduct human research. DHEW policies do not govern such research. Here too, the Federal Government's failure to develop a uniform policy has been detrimental to the welfare of research subjects.

2. Under current DHEW policies for the protection of research subjects, regulation of research practices is largely left to the biomedical professions. Since the conduct of human experimentation raises important issues of social policy, greater participation in decision-making by representatives of other professions and of the general public is required.

3. The present reliance by DHEW on the institutional review committee as the primary mechanism for the protection of research subjects was an important advance in the continuing effort to guarantee ethical experimentation. Prior peer review of research protocols is a requirement which should be retained.

4. The existing review committee system suffers from basic defects which seriously undermine the accomplishment of the task assigned to the committees:

a. The governing standards promulgated by DHEW which are intended to guide review committee decisions in specific cases are vague and overly general.

b. No provisions are made for the dissemination or publication of review committee decisions. Their low level of visibility hampers efforts to evaluate and learn from committee attempts to resolve the complex problems of human research.

c. Although the informed consent of the research subject is one of the most important requirements of research ethics, DHEW policies for obtaining consent are poorly drafted and contain critical loopholes. As a result, one crucial task of institutional review committees – the implementation of the informed consent requirement – is commonly performed inadequately. In particular, consent is far too often obtained in form alone and not in substance.

d. DHEW policies do not give sufficient attention to the protection of such special research subjects as children, prisoners and the mentally incompetent. The use of these subjects in human experimentation presents grave dangers of abuse.

e. The obligation of institutional review committees to conduct continuing review of research projects after their initial approval is undefined and as a consequence often neglected.

f. Inefficient utilization of institutional review committees contributes to their ineffectiveness. Committees are overburdened with a variety of separate functions, and could operate best if their tasks were narrowly defined to encompass mainly the implementation of research policies adequately formulated by others.

g. Effective procedures for enforcing DHEW policies, when those policies are disregarded, have not been devised.

5. No policy for the compensation of research subjects harmed as a consequence of their participation in research has been formulated, despite the fact that no matter how careful investigators may be, unavoidable injury to a few is the price society must pay for the privilege of engaging in research which ultimately benefits the many. Remitting injured subjects to the uncertainties of the law court is not a solution.

B. Policy Recommendations

1. Congress should establish a permanent body with the authority to regulate *at least* all Federally supported research involving human subjects, whether it is conducted in intramural or extramural settings, or sponsored by DHEW or other government agencies, such as the Department of Defense. Ideally, the authority of this body should extend to all research activities, even those not Federally supported. But such a proposal may raise major jurisdictional problems. This body could be called the National Human Investigation Board. The Board should be independent of DHEW, for we do not

believe that the agency which both conducts a great deal of research itself and supports much of the research that is carried on elsewhere is a position to carry out dispassionately the functions we have in mind. The members of the Board should be appointed from diverse professional and scientific disciplines, and should include representatives from the public at large.

2. The primary responsibility of the National Human Investigation Board should be to formulate research policies, in much greater detail and with much more clarity than is presently the case. The Board must promulgate detailed procedures to govern the implementation of its policies by institutional review committees. It must also promulgate procedures for the review of research decisions and their consequences. In particular, this Board should establish procedures for the publication of important institutional committee and Board decisions. Publication of such decisions would permit their intensive study both inside and outside the medical profession and would be a first step toward the case-by-case development of policies governing human experimentation. We regard such a development, analogous to the experience of the common law, as the best hope for ultimately providing workable standards for the regulation of the human experimentation process.

3. The National Human Investigation Board should develop appeals procedures for the adjudication of disagreements between investigators and the institutional review committees.

4. The National Human Investigation Board should also develop a "no fault" clinical research insurance plan to assure compensation for subjects harmed as a result of their participation in research. Institutions which sponsor Federally supported research activities should be required to participate in such a plan.

5. With the establishment of adequate policy formulation and review mechanisms, the structure and functions of the institutional review committees should be altered to enhance the effectiveness of prior review. In place of the amorphous institutional review committee as it now exists, we propose the creation of an Institutional Human Investigation Committee (IHIC) with two distinct subcommittees. The IHIC should be the direct link between the institution and the National Human Investigation Board, and should establish local regulations consistent with national policies. The IHIC should also assume an educational role in its institutions, informing participants in the research enterprise of their rights and obligations. The implementation of research policies should be left to the two subcommittees of the IHIC:

a. A Protocol Review Group (PRG) should be responsible for the prior review of research protocols. The PRG should be composed mainly of competent biomedical professionals.

b. A Subject Advisory Group (SAG) should be responsible for aiding subjects in their decision-making whenever they request its services. Subject must be made aware of the existence of the SAG. The primary concern of the SAG should be with procedures for obtaining consent, and with the quality of consents obtained. The SAG should be composed of both professionals and laymen.

III. DEVELOPMENT OF CURRENT DHEW POLICIES

A. Historical Background

Experimentation with human beings is not a modern phenomenon; it dates back to the beginning of recorded history. However, until the advent of scientific medicine, "research" was largely conducted unsystematically in the context of clinical practice which benefited, harmed or did nothing to untold patients. Indeed, harmful consequences most often accrued to countless patients who were given treatments whose value had not been established by carefully controlled clinical investigations.[6] Since the individuals involved in "research" were generally also considered potential recipients of the knowledge gained, few questions were raised about the propriety of these interventions by either the medical or legal profession. As far as the medical profession was concerned, the systematic use of human beings for research purposes, a trend which began in the late nineteenth century and has accelerated ever since, did not lead until relatively recently to a sustained exploration of the need to safeguard research subjects. A notable exception was Claude Bernard who in 1865 published his influential *An Introduction to the Study of Experimental Medicine,*[7] in which he not only demonstrated the need for experimentation on human subjects but also began to formulate rules of ethical conduct.

Similarly the law has had little to say about the rights of human subjects in the research enterprise. Indeed prior to the nineteen-sixties, no specific federal or state statutes regulated research institutions or investigators in their use of human subjects for experimental purposes. Though beginning with the English case of *Slater v. Baker and Stapleton*[8] in 1767 and the American case of *Carpenter v. Blake*[9] in 1871, courts were from time to time confronted with the claim of experimentation in malpractice actions, the resulting opinions evinced concern about "experimentation" but did not provide any meaningful legal guidelines for investigators to follow. Perhaps the fact situations in these cases, which often raised other important issues besides experimentation, precluded judges from speaking out more clearly on the legal limits to human research. Through the first third of the twentieth century, the generally accepted legal rule seemed to be that a physician experimented "at his peril" if his patients were harmed thereby.[10] Eventually, the distinction between rash human experimentation and careful, scientific and ethical experimental practice was acknowledged by the courts. In 1935, the Supreme Court of Michigan stated in a malpractice case:

> We recognize the fact that if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on; but such experiments must be done with the knowledge and consent of the patient or those responsible for him and must not vary too radically from the accepted method of procedure.[11]

Although this dictum was a broad generalization, made in a therapeutic context, and was not directed at nontherapeutic investigations, it signalled the ascendency of a more balanced judicial attitude toward medical research involving human beings.

This posture was sorely tested by the revelations of the horrifying atrocities perpetrated under the Nazis by German physicians and scientists in the name of clinical research.[12] The disclosures at Nuremberg disturbed the medical community, and many physicians and research scientists called for worldwide acceptance of ethical standards to assure the protection of subjects in biomedical research. However, the impact of their concern was blunted by the cruelty of the concentration camp experiments which obscured the fundamental fact that similar problems of research ethics, though not of the same magnitude, had characterized the research enterprise from its beginnings. Nonetheless, the trial of the Nazi physicians led the Military Tribunal to set forth ten basic principles, the so-called Nuremberg Code,[13] which must be observed in human experimentation "in order to satisfy moral, ethical, and legal concepts." The following principles illustrate the nature of the Code:

1. The voluntary consent of the human subject is absolutely essential. . . .
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods of study, and not random and unnecessary experiments in nature.

* * *

6. The degree of risk to be taken should never

6. See, e.g., Modell, "Let Each New Patient Be a Complete Experience," 174 J.A.M.A. 1717 (1960).

7. Bernard, *An Introduction to the Study of Experimental Medicine,* H. C. Greene (Transl.) (Macmillan, 1927).

8. 95 Eng. Rep. 860 (1767).

9. 60 Barb. 488 (N.Y., 1871).

10. See Curran, "Governmental Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," 98 Daedalus 542, 543 (1969).

11. Fortner v. Koch, 272 Mich. 273, 282; 261 N.W. 762, 765 (1935).

12. See *Trials of War Criminals Before the Nuremberg Military Tribunals. Volumes I and II, The Medical Case.* Washington, D.C.: U.S. Government Printing Office (1948). For excerpts which indicate the nature of the offenses and the resulting judgments, see Katz, *Experimentation with Human Beings,* pp. 292-306 (Russell Sage Foundation, 1972) (Hereinafter *Katz).*

13. *Katz, supra* footnote 12, at 305.

exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

The widely felt need to supplement and modify the provisions of the Nuremberg Code led to the proliferation of other "improved" codes of research ethics. The World Medical Association's Helsinki Declaration (1964),[14] the American Medical Association's Ethical Guidelines for Clinical Investigation (1966)[15] and the draft code of the American Psychological Association (1972)[16] are three which have received the most attention.

The promulgation of such documents helped to focus attention on the ethical problems inherent in research activities involving human subjects. However, as the number of documents increased their limitation become more evident to concerned observers. As one of us has elsewhere remarked:

> The proliferation of such codes testifies to the difficulty of promulgating a set of rules which do not immediately raise more questions than they answer. By necessity these codes have to be succinctly worded and, being devoid of commentary, their meaning is subject to a variety of interpretations. Moreover, since they generally aspire to ideal practices, they invite judicious and injudicious neglect. Consequently, as long as they remain unelaborated tablets of exhortation, codes will at best have limited usefulness in guiding the daily behavior of investigators.[17]

Furthermore, discrepancies between codes have helped to sow confusion. Discussing the Helsinki Declaration and the A.M.A. Guidelines, Professors Katz and Capron observed:

> The significant discrepancies between these two documents highlight the need for mechanisms which would permit their reconciliation. . . Unlike the Helsinki Declaration, the AMA guidelines propose that "(m)inors or mentally incompetent subjects may be used as subjects only if (t)the nature of the investigation is such that mentally competent adults would not be competent subjects." On the other hand, the Declaration of Helsinki states, and the AMA guidelines do not, that "(a)t any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued." No explanation is provided for the differences nor is any mechanism available to guide physician-investigators in adopting or rejecting part or all of either document, based on its disagreement with the other or for any additional reasons.[18]

In retrospect, the promulgation of so many varying codes of ethics can be viewed as a tacit recognition within the professions that self-regulation by investigators could not be relied on to control research practices. When it was also realized that the codes themselves had serious shortcomings, new and quite different proposals for ordering the research process began to emerge. Procedures were gradually developed to apply the general principles contained in codes of research ethics in the formal evaluation of individual research projects by institutional review committees.

The National Institutes of Health (NIH) first developed such procedures in order to regulate clinical research performed at its Clinical Center in Bethesda, Maryland. Since 1953, human research has not been conducted there without prior approval of a review committee responsible for the protection of subjects.[19] In 1966, Surgeon General William H. Stewart extended the requirement of prior review by "a committee of (the investigator's) institutional associates" to all "extramural" research supported by United States Public Health Service (PHS) grants and awards.[20] This review was to

> assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation.[21]

Prior committee review was also instituted, in 1967, for all "intramural" research programs of the Public Health Service.[22] The Tuskegee Syphilis Study, conducted by PHS investigators, was an intramural activity.

14. 271 N. Eng. J. Med. 473 (1964).

15. American Medical Association, *Opinions and Reports of the Judicial Council,* pp. 9-11 (Chicago, 1969).

16. American Psychological Association, *Ethical Principles in the Conduct of Research with Human Participants* (Draft Document, 1972).

17. Katz, "The Education of the Physician-Investigator," 98 *Daedalus* 480, 482-3 (1969).

18. Katz and Capron, *Social Factors Affecting the Modern Treatment of Catastrophic Diseases* (Unpublished Manuscript, 1973) (hereinafter, *Katz and Capron).*

19. Sessoms, "Guiding Principles in Medical Research Involving Humans, National Institutes of Health," 32 *Hospitals, Journal of American Hospital Association* 44 (1958).

20. Memorandum of Surgeon General William H. Stewart to the Heads of Institutions Conducting Research with Public Health Grants, (February 8, 1966).

21. *Ibid.*

22. DHEW – Public Health Service, *Protection of the Individual as a Research Subject* – Intramural Programs (May 1, 1969) (hereinafter *Intramural Guidelines).*

In 1971, the Department of Health, Education, and Welfare formulated its policy for the protection of human subjects[23] which superseded the Public Health Service extramural program guidelines. Institutional committee review was retained as the central feature of the new DHEW policy. The DHEW regulations apply to all research supported by Departmental grants or contracts, regardless of whether the research is medical in nature. However, the new regulations do not apply to intramural PHS activities, which are still governed by separate and sometimes divergent PHS guidelines. Also in 1971, the Food and Drug Administration promulgated additional regulations,[24] patterned on the DHEW framework, to govern the testing of "investigational new drugs." And recently, in response to the Tuskegee Syphilis Study revelations, Senator Jacob Javits introduced a bill which would enact most of the current DHEW requirements into law.[25] Senator Hubert Humphrey also responding to the Tuskegee Study, introduced another bill, quite different in conception.[26] It would create within the executive branch an independent board to establish guidelines for human experimentation, to review research practices and to enjoin the conduct of certain investigations.

Due to the Federal Government's prominent role in funding biomedical research, the PHS-DHEW regulations have had a noticeable impact on the conduct of human research in this country. Over 700 American research institutions have established review committees in order to satisfy DHEW or PHS requirements.[27] Although these committees are required to review only Federally-funded research, they often have extended their review to all research on human subjects conducted at their institutions.[28]

B. Description of DHEW Policy[29]

At present DHEW policies vest primary responsibility for the protection of research subjects in institutional review committees. These committees are charged with the initial review of all project proposals and are also expected to subject research activities to "continuing review." Once a committee has approved a research protocol, its decision is reviewed again by the DHEW study section which considers the protocol for funding. When either group disapproves a protocol, that decision cannot be appealed to the Department, and the protocol cannot be Federally funded. In contrast to the DHEW requirements, PHS intramural policy does not require continuing review. Instead, the burden is on the investigator to bring "significant proposed changes in protocol and emergent problems of investigation. . .to the attention of the review group involved."[30] Nor does PHS intramural policy specify distinct stages of protocol review.

DHEW requires institutional committees to review all aspects of "any activity" which might expose a subject to the possibility of harm if the activity "goes beyond the application of those established and accepted methods necessary to meet his needs."[31] Recognizing that this jurisdictional standard leaves much to the discretion of committees and investigators the Department concedes that "(a)cceptance is a matter of professional response, and determination as to when a method passes from the experimental stage and becomes 'established and accepted' is a matter of judgment."[32]

Before the committee can approve an activity under review, it must "determine that the rights and welfare of the subjects involved are adequately protected, that the risks to an individual are outweighed by the potential benefits to him or by the importance of the knowledge to be gained, and that informed consent is to be obtained by methods that are adequate and appropriate."[33] Like the jurisdictional standard, these review standards are phrased in general terms, although the "basic elements" of "informed consent" are set forth in greater detail.[34] DHEW policy also requires each institution to provide written assurance that it will abide by DHEW policy. The assurance must include "a statement of compliance with DHEW requirements for initial and continuing committee review of the supported activities; a set of implementing guidelines, including identification of the committee, and a description of its review procedures."[35] As part of the "implementing guidelines," each institution is asked to adopt a "statement of principles that will assist the institution in the discharge

23. DHEW Grants Administration Manual Chapter 1-40 (1971) (hereinafter *Grants Administration Manual*). The Department publishes *The Institutional Guide to DHEW Policy on Protection of Human Subjects* (1971) (hereinafter *Institutional Guide*) to help institutions sponsoring research to implement DHEW policy.

24. 36 Fed. Reg. 5037-38 (1971).

25. S. 3935, 92d Cong., 2d Sess. (1972).

26. S. 3951, 92d Cong., 2d Sess. (1972).

27. For a description of the spread of institutional review committees following the promulgation of the PHS guidelines, see *Barber et al., supra*, footnote 3, at 145-148.

28. Barber *et al.* estimate that 85% of the institutional review committees they surveyed review "all clinical research" conducted at their institutions, regardless of funding. *Barber et al., supra*, footnote 3, at 149.

29. This description is based on the *Intramural Guidelines, supra*, footnote 23, and the *Institutional Guide, supra*, footnote 23. Hereinafter, the policy of the Manual and the Guide will be referred to as "DHEW" policy, while the policy of the Intramural Guidelines will be referred to as "PHS intramural" policy.

30. *Intramural Guidelines, supra*, footnote 22, at 5.

31. *Grants Administration Manual, supra*, footnote 23, § 1-40-10.

32. *Institutional Guide, supra*, footnote 23, at 3.

33. *Grants Administration Manual, supra*, footnote 23, § 1-40-20(A). The PHS *Intramural Guidelines, supra*, footnote 22, contain essentially equivalent standards for review, at 4-5.

34. See *infra.*, pp. 31-32.

35. *Grants Administration Manual, supra*, footnote 23, § 1-40-40 (A).

36. *Grants Administration Manual, supra*, footnote 23, § 1-40-40 (C) (2) (a).

37. *Ibid.* See also *Institutional Guide, supra*, footnote 23, at 5, footnote 2, and at 23.

of its responsibilities for protecting the rights and welfare of subjects."[36] These statements are typically derived from existing codes of ethics not much more explicit that the DHEW review standards themselves.[37]

Unlike DHEW policy, the intramural guidelines of the PHS make specific, albeit limited, reference to "(s)tudies involving children, the mentally ill or the mentally defective."[38] Such studies "shall be carried out only when there is no significant risk of physical or mental harm to the subject or when direct benefit to the subject is anticipated."[39] The intramural guidelines also explicitly provide that "(s)tudies of individuals with limited civil freedom shall also be subject to group consideration and approval."[40] Although the references to minors, incompetents, and prisoners do not impose additional substantive restrictions on research, they may alert review committees and investigators to the special problems presented by research with such subjects.[41]

Since institutional review committees are entrusted with such difficult decision-making responsibilities, their composition is a matter of Departmental concern:

> The committee must be composed of sufficient members with varying backgrounds to assure complete and adequate review of projects and activities commonly conducted by the institution. The committee's membership, maturity, experience, and expertise should be such as to justify respect for its advice and counsel. No member of an institutional committee shall be involved in either the initial or continuing review of an activity in which he has a professional responsibility, except to provide information requested by the committee. In addition to possessing the professional competence to review specific activities, the committee should be able to determine acceptability of the proposal in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The committee may therefore need to include persons whose primary concerns lie in these areas rather than in the conduct of research, development, and service programs of the types supported by the DHEW.[42]

Beyond this, the Department does not specify any particular size or membership requirements, believing instead that disparity in institutional situations demands flexibility. For the same reason the Department does not provide any directions for the conduct of initial or continuing review. Instead, as already noted, institutions are required to submit for Departmental approval a description of the procedures their committees will follow to implement review.

When DHEW funding is sought, a research proposal approved by an institutional committee is reviewed again within the Department.[43] A study section, composed of scientists not connected with the proposal or its sponsoring institution, examines the proposal and transmits its recommendation to the particular National Advisory Council authorized to grant the requested research funds. This Departmental review is not restricted to a reconsideration of the "ethical soundness" of the proposed research. Instead, it encompasses all other factors which enter into any research funding decision, such as the scientific rigor of the proposal, the scientific significance of the proposed project, and the relationship of budgetary estimates to the proposed study. As a result, the review of ethical issues at this stage cannot be as thorough as it is intended to be at the institutional level.

The adoption of this institutional review committee approach promised to be a significant advance toward the goal of ethical human research. For the first time, codes of research ethics were to be applied in concrete situations by means of a definite procedure providing for independent scrutiny of individual research proposals. Moreover, a decentralized, pluralistic approach, emphasizing decision-making at the institutional level, seemed to offer other advantages. The exploration of problems from different points of view could ultimately lead to a fuller appreciation of the issues requiring resolution. Concern for the rights and welfare of subjects could be more easily communicated to individual investigators. The review of research protocols could be handled in depth and yet with dispatch.

Despite these hopes, the present DHEW regulatory framework can only be considered a qualified success. The continued existence of two varying sets of guidelines to govern intramural and extramural human research activities respectively serves no purpose and generates confusion. As to the content of the guidelines, although from a historial perspective institutional committee review was a major improvement over prior practices, many deficiencies, to which we now turn, have precluded successful supervision of human experimentation for the protection of human subjects.

38. *Intramural Guidelines, supra,* footnote 22, at 10.
39. *Ibid.*
40. *Ibid.*
41. PHS intramural policy does impose stricter consent requirements for experiments with such subjects. These consent requirements are discussed *infra,* at pp. 25 ff.
42. *Grants Administration Manual, supra,* footnote 23, §1-40-40 (C) (2) (b).
43. *Grants Administration Manual, supra,* footnote 23, §§1-40-20 (B) and 1-40-50 (B). See also NIH Manual §4107 "Grants Involving Human Subjects," §4107 (G) (1972).

IV. CRITIQUE OF DHEW POLICY

A. Vagueness of Standards

At bottom, the difficulties which face review committees derive from the generality of the standards which are to guide their determinations in specific cases under either the intramural or extramural policies. To illustrate, if a review committee had evaluated the Tuskegee Syphilis Study under current guidelines, questions calling for searching examination would have surfaced.

(1) If the requirement of informed consent[44] is to be taken seriously, should impoverished and uneducated Blacks from rural Alabama have been selected as subjects in the first place? Or should a concerted effort have been made to find subjects from among the most educated within the population at large, or at least to select from the given subgroup those subjects most capable of giving "informed consent"? Put more generally, what general principles should guide the selection of subjects? The philosopher Hans Jonas has given one answer to this question: "(O)ne should look for (subjects) among the most highly motivated; the most highly educated, and the least 'captive' members of the community."[45]

(2) If "(t)he welfare of the individual is paramount (and) the subject must have available to him the facilities and professional attention necessary for the protection of his health and safety,"[46] what special efforts should have been made by investigators to provide medical treatment beyond the economic reach of the subjects before enlisting them in the Tuskegee Study? Or should the institutional review committee have turned down the Tuskegee Syphilis Study because no adequate treatment facilities were available in Macon County?

(3) How should "continuing review" operate? For example, at what point in time, after penicillin treatment for syphilis became available, should the subjects of the Tuskegee Syphilis Study have been apprised of this new development? Since it generally takes time before medical consensus is reached on the value of a new medication and is reported in the medical literature, when should the subjects have been told that a drug was available which at least some competent physicians considered effective treatment?

(4) How should the risks inherent in this study have been weighed against the predicted advancement of medical knowledge? The rule that "the risks to an individual. . .(must be) outweighed by the potential benefits to him or by the importance of the knowledge to be gained,"[47] is perhaps the most difficult guideline for review committees to implement. The seeming simplicity of this command belies its complexity. How are such tangibles as "risks," "benefits," and "importance of knowledge" to be measured and weighed? Can serious harm to research subjects ever be outweighed solely by additions to the sum of human knowledge?[48] If so, what kind of knowledge, in what circumstances, would outweigh what risks to subjects? The difficulties inherent in evaluating the scientific merits of a particular study are demonstrated by the ongoing differences of opinion among scientists of the PHS as to whether continuation of the Tuskegee Syphilis Study can still be defended on the ground of scientific merit. It is necessary for review committees to scrutinize carefully the research design of every proposed study if the requirement that risks be balanced against benefits is to be taken seriously, for the acquisition of knowledge depends so much on the soundness of the research protocol.[49] Does the informed willingness of the subject to accept certain risks have any bearing on the committee's balancing of risks against benefits? Finally, since the design of the Tuskegee Study could not completely exclude the possibility that non-subjects might contract syphilis from untreated subjects, how should a review committee have balanced risks to nonsubjects against benefits to society?[50]

(5) Review committees are also required to "determine that the rights and welfare of the subjects involved are adequately protected."[51] What rights did the Tuskegee Study subjects possess? The tremendous confusion which exists in the area of patient subjects' rights is in part the result of the traditional but largely unexamined prerogative of professionals

44. The requirement of informed consent is analyzed in greater detail *infra*, at pp.31 ff.

45. Jonas, "Philosophical Reflections on Experimenting with Human Subjects," 98 *Daedalus* 219, 235 (1969).

46. *Intramural Guidelines, supra*, footnote 22, at 1.

47. *Grants Administration Manual, supra*, footnote 23, §1-40-20 (A); see also *Intramural Guidelines, supra*, footnote 22, at 2, 4-5.

48. Although PHS policy does proscribe seriously risky experimentation which cannot benefit the subject, *Intramural Guidelines, supra*, footnote 22 at 2, DHEW policy for extramural research does not categorically prohibit such research. The *Institutional Guide, supra*, footnote 23, states at 6: "If the potential benefits are insubstantial, or are outweighed by risks, the committee may be justified in permitting the subjects to accept these risks in the interests of humanity."

49. *Intramural Guidelines, supra*, footnote 22, at 1.

50. The *Intramural Guidelines, supra*, footnote 22, at 1, state: The health and safety of persons other than the subject, if endangered by the research procedures, must be protected. DHEW policy neglects this problem.

51. *Grants Administration Manual, supra*, footnote 22, §1-40-20 (A); see also *Intramural Guidelines, supra*, footnote 22, at 1, 4-5.

to intervene in their patients' behalf without full disclosure whenever it is supposed to be "in their patients' best interests." The doctrine of "informed consent" has had little impact on this longstanding professional practice. Since much medical research is carried out in the context of "patient care" the right to make decisions for patients has more often than not unwittingly been carried over into the research domain. The confusion about patient-subjects' rights is bolstered by the scientist's felt obligation to advance knowledge for the good of society, although society has inadequately defined the extent of this obligation.

To illustrate the confusion about subject's rights: Can the subject claim the right to be indemnified for any harm he suffers as a result of the research, regardless of the investigator's fault and in spite on consent? Is so, who is responsible for informing him that an injury has occurred which is not the result of the natural progression of his illness? Do Tuskegee Study subjects have a cause of action because they did not receive suitable medical treatment? If so, who may be liable–the individual investigators, the PHS, the Milbank Memorial Fund, the Tuskegee Institute? The intramural guidelines of the PHS and *The Institutional Guide to DHEW Policy on Protection of Human Subjects* also identify confidentiality as a right which must be protected.[52] Does confidentiality extend only to the subject involved in the study or does it also include the group of which he is a part? If the latter, what are the limits of group confidentiality? The Tuskegee Syphilis Study, in common with many other studies, singled out one particular group and revealed much that was intimate and private about all its members. Where can review committees seek guidance in devising procedures which safeguard subjects' rights in general, and their rights to confidentiality, privacy and respect, in particular?[53]

(6) The jurisdiction of institutional review committees encompasses "any activity which goes beyond the application of those established and accepted methods necessary to meet. . (the subject's) needs."[54] How are "established and accepted" methods to be ascertained? Among "established" treatments should distinctions be made between those of "proven" and those of "dubious" value? What are the criteria for a "necessary" intervention? Since there is so much professional disagreement as to when a procedure becomes "therapeutic," the question must be posed: "accepted" by whom? Was the withholding of arsenic and heavy metal treatments at the beginning of the Tuskegee Study a "therapeutic" intervention since the effectiveness of such treatments was in doubt, particularly for late syphilis? When did penicillin treatment become an "established and accepted method"? What degree of certainty is required of investigators and review committees? Certainly no clear line can be drawn between experimental and routine treatment since, as has so frequently been asserted, "the therapy of disease is, and always will be, an experimental aspect of medicine."[55]

The vagueness and generality of the governing standards have disadvantaged all participants in the research decision-making process. For conscientious review committees, they have meant hard work and, insofar as the committees are overwhelmed by the enormity of their task, superficial examination of protocols. For subjects, the inevitable result has been to deprive them in some measure of the protection which review committees were supposed to provide. For investigators, the pervasive uncertainty about what kind of human studies are now permissible has impeded their research. And for society, fears about the protection of its citizens in the research enterprise have not been stilled. Especially because review committees work in isolation from one another and no mechanisms have been provided for disseminating the knowledge gained from their individual experiences, each committee is condemned to repeat the process of finding their own answers to all the questions we have raised. This is an overwhelming, unnecessary and unproductive task for which they are not prepared and which we doubt they are willing to assume.

What is needed, is an overall official body authorized to formulate more detailed policies with respect to research on human beings. The need for such a policy making body has in point of fact already been perceived, and other bodies, official and non-official, have partially and on an *ad hoc* basis attempted to fill the gap. For example, the FDA has promulgated comprehensive rules for the conduct of drug research,[56] although on many crucial issues of subject protection it has simply copied DHEW policy.[57] Similarly, in the wake of organ transplantation, an *ad Hoc* Committee of the Harvard

52. *Intramural Guidelines, supra,* footnote 22, at 9; *Institutional Guide, supra,* footnote 23, at 6.

53. The *Institutional Guide, ibid.,* does make an effort to suggest procedures for safeguarding confidentiality.

54. *Grants Administration Manual, supra,* footnote 23, § 1-40-10 (B); see also *Intramural Guidelines, supra,* footnote 22, at 2-3, 7-8.

55. Ivy, "The History and Ethics of the Use of Human Subjects in Medical Experiments" 108 *Science* (July, 1948). Barber *et al.* have recently documented the prevalence of professional uncertainty over the definition of "research." See *Barber et al., supra,* footnote 3 at 150.

56. See 21 C.F.R. § § 130.3, 130.37.

57. *Ibid.*; see also 36 Fed. Reg. 5037 (1971).

Medical School redefined the criteria of "death" in order to facilitate the removal of needed organs.[58] Moreover, the Division of Research Grants of NIH,[59] which at present supervises the implementation of DHEW policy, has occasionally transmitted memoranda to review committees "concerning the interpretation and implementation of (its) policy."[60] Recent memoranda focused on potential hazards of screening programs for sickle cell trait, the definition of "human subject," and guidelines for fetal studies. These policy making activities need to be consolidated, under the auspices of a broadly representative body, about which we shall have more to say below. Such a body would not only provide guidance to review committees but would also enable them to obtain advice whenever difficult problems arise.

B. Invisibility

The creation of institutional review committees could have led to increased visibility of decisions regarding the protection of subjects. But since neither publication nor free access to their findings was specifically planned for, increased visibility has not been realized. A low level of visibility hampers efforts to evaluate and learn from attempts to resolve the complex problems of human research. Especially so long as guidelines for human research remain so indefinite, high-visibility decision-making is an essential feature of a well-functioning regulatory framework. Moreover, since committee disapprovals can block research, with no recourse to higher level review, invisibility may impede the acquisition of valuable knowledge.

The 1969 committee review of the Tuskegee Syphilis Study illustrates the problems which a low level of visibility creates. Our knowledge of that proceeding comes from an unofficial summary which constitutes the only available report on that committee's deliberations. From this summary it is impossible to determine the factors which the committee considered or the grounds on which the committee based its decision to approve a continuation of the study. This state of affairs is not atypical. Because institutional committee decisions are not published, committee decision-making operates at a primitive level, uninformed by pertinent prior decisions of other committees or by scholarly outside criticism. A mechanism for self-improvement over time is lacking. Professor Guido Calabresi has observed:

> . . .The best way of broadening the imputs to the committee–lies in another device: publication of the cases decided by the committees. Such cases could well be anonymous (at least at first). They could be collected and published in much the same way that decisions of courts are collected. The reports on any case could include, first a factual part describing, among other things, the experience of the experimenter, the antecedent tests in non-human subjects, the major risks perceived, the scientific gains perceived possible, the availability of subsequent controls to limit the risks, the origin and life expectancy of the subjects, and the nature of the consent and the manner in whcih it was obtained; and, second, a jurisprudential section containing the decision of the committee (whether favorable or unfavorable), together with the principal arguments made for and against the decision reached.
>
> Such published cases would soon become the subject of intense study both inside and outside the medical profession. Analyses in learned journals by lawyers, doctors, and historians of science would inevitably follow. These would undoubtedly re-argue the more important or path-breaking cases. If law cases are any guide, the analyses would sometimes conclude that the cases were wrongly decided, but frequently that they were rightly decided, and perhaps more frequently that they were rightly decided but for the wrong reasons. To the extent that Law Reviews consider themselves courts of last appeal beyond the highest courts in the land, so would the learned journals in which this *giurisprudenza* would be dissected. From all this, a sense of what society at large deems proper in medical experiments might well arise. This sense would, in turn, guide the committees and make their decisions more sophisticated. The result would not only be better thought out decisions, but also a more complex system of controls, which, in effect, took into account much broader sources of information as to societal values. . . .[61]

In the Recommendation section of our report we incorporate Calabresi's suggestions in a comprehensive framework for the regulation of human experimentation.

C. Subject Consent

1. The Definition of "Informed Consent"

Institutional review committees are expected to

58. *Ad Hoc* Committee of the Harvard Medical School, "A Definition of Irreversible Coma," 205 J.A.M.A. 337 (1968).

59. *Grants Administration Manual, supra,* footnote 23, § 1-40-50 (A).

60. Memorandum of January 24, 1972, from Stephen P. Hatchett, Director, Division of Research Grants, NIH, DHEW, to Officers Responsible for Institutional Implementation of DHEW Policy on Protection of Human Subjects.

61. Calabresi, "Reflections on Medical Experimentation in Humans," 98 *Daedalus* 387, 400-401 (1969).

ascertain "that informed consent is. . .obtained by methods that are adequate and appropriate."[62] The DHEW Grants Administration Manual, in contrast to its treatment of other important matters, defines "informed consent" in some detail:

> Informed consent is the agreement obtained from a subject, or from his authorized representative, to the subject's participation in an activity.
>
> The basic elements of informed consent are:
>
> 1. A fair explanation of the procedures to be followed, including an identification of those which are experimental;
> 2. A description of the attendant discomforts and risks;
> 3. A description of the benefits to be expected;
> 4. A disclosure of appropriate alternative procedures that would be advantageous for the subject;
> 5. An offer to answer any inquiries concerning the procedures;
> 6. An instruction that the subject is free to withdraw his consent and to discontinue participation in the project or activity at any time.[63]

The PHS Intramural Guidelines also explicate informed consent in some detail:

> The individual must be free to choose whether or not to be a subject in research. His participation shall be accepted only after he has received a fair explanation of the procedures to be followed, benefits, and attendant hazards and discomforts, and, suited to his comprehension, the reasons for pursuing the study and its general objectives. He must be informed of his right to withdraw from the study at any time.[64]

For no apparent reason, two "basic elements" of informed consent identified in DHEW policy are ignored by the PHS intramural policy. Nothing is said in the intramural policy statement about disclosure of alternative procedures ("basic element" number four) or response to inquiries ("basic element" number five).

Despite the commendably greater detail with which DHEW policy on obtaining informed consent is set forth, major gaps do remain. For instance, the DHEW directives permit consent to be obtained from the subject's "authorized representative" in lieu of the subject himself. But the circumstances in which third party consent may properly be substituted for the consent of subjects are undefined. Committees are not advised as to who can validly consent in place of the subject or whether consent can be obtained from another person besides the subject only for certain investigations, such as those specifically designed to benefit the subjects themselves. Thus, committees are left to their own devices in fashioning rules about the participation in research of such subjects as the very young or the very old, the mentally incompetent or the emotionally disturbed, the imprisoned or those otherwise under duress, or, as in the Tuskegee Study, those who are ill-prepared as a consequence or cultural deprivation or inadequate education.

In contrast to the DHEW extramural guidelines, the PHS intramural research rules do address the problems of substitute consent for special subjects in more detail:

> Studies involving children, the mentally ill or the mentally defective should be carried out only when there is no significant risk of physical or mental harm to the subject or when direct benefit to the subject is anticipated. . . . In general, written informed consent of the parent or guardian shall be required for all medical or dental studies with such subjects, except in studies of an observational nature or in those conducted during the administration of accepted health care procedures that do not require specific informed consent in ordinary practice. Any exception shall be carefully considered and fully documented. Written informed consent of parent or guardian may be desirable in certain other studies with these groups and shall be required if conditions warrant. . . . Studies of individuals with limited civil freedom shall also be subject to group consideration and approval. Informed consent of the responsible institutional authority shall be required in all cases. Written informed consent of the individual shall also be required except for studies of an observational nature conducted during the administration of accepted health care procedures that do not require specific informed consent in ordinary practice.[65]

The major difficulties with these provisions result from the exceptions to the general requirement of substitute consent. "Studies of an observational nature" and "accepted health care procedures that do not require specific informed consent in ordinary practice" are phrases too vague to be meaningful. For example, was the Tuskegee Syphilis Study "of an observational nature"? In what "other" kinds of studies may investigators dispense with the consent of parent or guardian unless unspecified "conditions warrant" it?

62. *Grants Administration Manual, supra,* footnote 23, § 1-40-20 (A).
63. *Grants Administration Manual, supra,* footnote 23, § 1-40-10 (C).
64. *Intramural Guidelines, supra,* footnote 22, at 1.
65. *Intramural Guidelines, supra,* footnote 22, at 10-11.

Moreover, the PHS instructions ignore the issue of the capacity of third parties to represent the interests of special subjects adequately, and the subtle inducements which may persuade prisoners to consent.

Prisoners in particular are a group whose participation in research has long been controversial.[66] Because prisoners are a captive group, the danger is great that their consent to participate in research will be obtained by duress. Jessica Mitford has recently documented some of the abuses to which prisoner participants in experimentation have been subjected, and she comments:

> The (Institutional) Guide expresses a "particular concern" for "subjects in groups with limited civil freedom. These include prisoners. . . ." Having uttered this praiseworthy sentiment, HEW has apparently let the matter drop. Dr. D.T. Chalkley, chief of the Institutional Relations Branch, Division of Research Grants, and signer of the Guide, tells me that HEW does not even maintain a list of prisons in which HEW-financed research programs are in progress and has "no central source of information" on the scope of medical experiments on prisoners by drug companies. . . .
>
> What efforts have been made by HEW to enforce its guidelines in HEW-financed medical research behind prison walls? "We do give some grants that involve prisoners. But there's no convenient way of recovering the information as to whether our guidelines are being followed," said Dr. Chalkley. "That responsibility lies with the principal investigator. . . ." has HEW ever brought any action to enforce its regulations in any prisons anywhere? "None, to date."[67]

Most new drug testing is initially conducted on prisoners, and is subject to FDA regulations, but the FDA also has no list of persons in which such research is carried out.[68]

We regard the failure of the DHEW policies to include comprehensive guidelines for safeguarding prisoners, children, mental incompetents, and other special subjects in research, as a major shortcoming which must be rectified. Detailed policy must be formulated specifying the kinds of research which may be carried out with special subjects of different types, the inducements which are permissible, the circumstances in which third-party consent is necessary, the identity of those who can validly consent for the subject, additional precautions which must be taken for such subjects, and other matters.

2. Exceptions to the Consent Requirement

In its *Institutional Guide to DHEW Policy on the Protection of Human Subjects,* the Department sets forth the following additional exceptions to the requirement of informed consent:

> The review committee will determine if the consent required, whether to be secured before the fact, in writing or orally, or after the fact following debriefing, or whether implicit in voluntary participation in an adequately advertised activity, is appropriate in the light of the risks to the subject, and the circumstances of the project.
>
> Where an activity involves therapy, diagnosis, or management and a professional/patient relationship exists, it is necessary "to recognize that each patient's mental and emotional condition is important. . .and that in discussing the element of risk, a certain amount of discretion must be employed consistent with full disclosure of fact necessary to any informed consent."[69]

The first exception which permits obtaining consent "after the fact," is so general in scope and so extensive in the discretion it accords review committees that it almost staggers the imagination. What are "the circumstances of the project" which could ever permit such an invasion of subjects' rights to self-determination and privacy? Is this exemption limited to investigations with normal subjects employing placebos or to deception studies so frequently employed by psychologists? In one sentence the requirement of prior[70] informed consent is seriously undermined.

Furthermore, another exception provides for a departure from informed consent in situations in which "a professional/patient relationship exists." Since most medical research is carried out in such settings, it can apply to almost all medical interventions. It is particularly in clinical settings that overreaching in obtaining consent, however unwitting, is a constant danger.[71] Thus the unqualified provision that "a certain amount of

66. See, e.g., Lasagna, "Special Subjects in Human Experimentation," 98 *Daedalus* 449 (1969); *Katz, supra,* note 12, pp. 1018-1052; Mitford, "Experiments Behind Bars," *The Atlantic Monthly* 64 (January, 1973).

67. Mitford, "Experiments Behind Bars," *supra,* footnote 67, at 67-68.

68. See Mitford, "Experiments Behind Bars," *supra,* footnote 67, at 68.

69. *Institutional Guide, supra,* footnote 23, at 8.

70. It is implicit that consent is normally to be obtained prior to the subject's participation in research, although DHEW policy nowhere so states.

71. See *infra,* pp. 40ff.

discretion must be employed consistent with full disclosure of fact" is particularly unsatisfactory.[72]

PHS intramural policy also contains loopholes in its consent provisions. First, the guidelines state that

> An explanation so detailed as to bias his response or otherwise to invalidate findings is not necessary in those procedures that involve no risk of physical harm to the subject.[73]

This qualification is apparently designed to minimize interference with behavioral and other studies common to the social sciences. This guidelines elsewhere state that

> a major class of procedures in the social and behavioral sciences does no more than observe or elicit information about the subject's status by means of tests, inventories, questionnaires or surveys of personality or background. In such instances, the ethical considerations of voluntary participation, confidentiality, and propriety in use of the findings are the most generally relevant ones. The procedures may in many instances not require the fully informed consent of the subject or even his knowledgeable participation.[74]

The lack of concern in the quoted passages for psychological–as opposed to physical–harm to subjects is striking. Despite acknowledged ethical problems, the guidelines suggest that in "many instances" the "knowledgeable participation" of the subject may be unnecessary. Here again, the regulations fail to provide meaningful guidance to review committees.

3. The Quality of "Informed Consent"

Another difficulty which seriously undermines the implementation of informed consent has not been dealt with at all in the DHEW policies. It has long been recognized that consent is far too often obtained in form alone, and not in substance. As the Department itself admits in its Institutional Guide (quoting Doctor Henry K. Beecher of Harvard Medical School):

> "The informed consent of the subject, while often a legal necessity is a goal toward which we must strive, but hardly ever achieve except in the simplest cases."[75]

For as Doctor Beecher has written elsewhere,

> Lay subjects, sick or well, are not likely to understand the full implications of complicated procedures, even after careful explanation.[76]

Even with the best of intentions, investigators may fail to "get through" to their subjects for a variety of reasons. The subjects themselves may have great difficulty in understanding or little interest in knowing the nuances of what the investigator tries to explain to them. As Senator Hubert Humphrey recently lamented in response to the Tuskegee Syphilis Study:

> Who are the people who have been the subjects of medical experiment? The clear and shocking implications of the most recently revealed experiments indicate that the powerless, the poor, the least educated, and members of minority groups are the likeliest human guinea pigs. . . .
>
> It is those who cannot understand what is being done to them that constitute by far the largest numbers among human experimentation subjects.[77]

Moreover, the circumstances in which consent is sought may foster or hinder an informed and voluntary decision. The subject may be under stress or distracted by other pressing concerns. For example, he may be a patient, desperately hoping for successful treatment of his condition, whose judgment is distorted by the natural tendency to grasp at any straw in reach. The likelihood of this result is magnified by the profound dependence which many patients develop on their attending physicians, who are often responsible for obtaining consent. Indeed, however wrongly, the patient may well fear that his refusal to consent to experimental

72. Compare the more satisfactory provisions on informed consent adopted by the FDA, 21 CFR § 130.37, which require that consent be obtained "in all but exceptional cases." This is defined as follows:

> (d) "Exceptional cases," as used in paragraph (b) of this section, which exceptions are to be strictly applied, are cases where it is not feasible to obtain the patient's consent or the consent of his representative, or where, as a matter of professional judgment exercised in the best interest of a particular patient under the investigator's care, it would be contrary to that patient's welfare to obtain his consent.
>
> * * *
>
> (f) "Not feasible" is limited to cases where the investigator is not capable of obtaining consent because of inability to communicate with the patient or his representative; for example, where the patient is in a coma or is otherwise incapable of giving informed consent, his representative cannot be reached, and it is imperative to administer the drug without delay.
>
> (g) "Contrary to the best interests of such human beings" applies when the communication of information to obtain consent would seriously affect the patient's disease status and the physician has exercised a professional judgment that under the particular circumstances of this patient's case, the patient's best interests would suffer if consent were sought.

73. *Intramural Guidelines, supra,* footnote 22, at 1-2.

74. *Intramural Guidelines, supra,* footnote 22, at 9.

75. *Institutional Guide, supra,* footnote 23, at 7.

76. Beecher, *Research and the Individual* (Little, Brown and Co. 1970).

77. 118 Cong. Rec. S 14041 (Sept. 5, 1972). Senator Humphrey's assertion is corroborated by the recent study of research practices conducted by Barber *et al.* In the two institutions they analyzed, they found that studies in which the risks were relatively high in proportion to therapeutic benefits to the subjects were "almost twice as likely as more favorable studies to be done using subjects more than three-fourths of whom (were) ward and/or clinical patients," as opposed to private and/or semi-private patients. Moreover, this proportion is not significantly altered when studies in which the risk exceeds all possible benefits, to the subjects or to medicine generally are examined: "the 'least favorable' studies (were) still almost twice as likely as the more favorable to be done using three-fourths or more ward or clinical patients." *Barber et al., supra,* footnote 3 at 55, 56.

treatment will anger his physician and deprive him of adequate medical care.

Lastly, the investigator himself may fail to describe his own research objectively, or unwittingly create subtle pressures on a subject to consent. To suggest this is not to deny the integrity of the researcher, but only to acknowledge the reality of investigators' bias toward their work. Their scientific curiosity and excitement make it difficult for them to take a detached view of the research they wish to conduct with their subjects.

D. Continuing Review

Although extramural research projects supported by DHEW grants or contracts must be reviewed on a continuing basis, intramural research activities of the Public Health Service need not be reviewed again after initial committee approval. This omission for intramural programs of what the Department itself calls "an essential part of the review process"[78] explains the long neglect of the Tuskegee Study. Begun long before committee review became a reality, the Study was not reviewed by any committee until 1969, three years after Surgeon General Stewart had inaugurated the policy of committee review. Moreover, the 1969 review was undertaken at the behest of the principal investigators themselves, and not as the result of the Public Health Service review policy. The Tuskegee Study was not reviewed again until this Panel was appointed. We have been unable to ascertain why intramural research programs are exempt from the continuing review requirement.

Although DHEW extramural policy does require "continuing review," a better definition of the nature and extent of this obligation is needed. The present indefinite regulations invite a perfunctory performance of the continuing review function. Essentially the Department expects that the committees will

> . . . adopt a variety of continuing review mechanisms. They may involve systematic review of projects at fixed intervals, or at intervals set by the committee commensurate with the project's risk. Thus, a project involving an untried procedure may initially require reconsideration as each subject completes his involvement. A highly routine project may need no more than annual review. Routine diagnostic service procedures, such as biopsy and autopsy, which contribute to research and demonstration activities generally require no more than annual review. Spot checks may be used to supplement scheduled reviews. Actual review may involve interviews with the responsible staff, or review of written reports and supporting documents and forms. . .[79]

Institutional review committees, already overburdened by the task of examining all new research projects, are thus also responsible for re-examining from time to time all ongoing research. If something has to give first, it tends to be this assignment. Pressed for time, the review committees assume that the initial review has satisfactorily resolved all existing problems and that a cursory review is sufficient.

E. Structure and Composition of Institutional Committees

Institutional review committees are charged with carrying out a number of distinct functions. They are required to formulate policies and regulations to guide the conduct of research at their institutions,[80] often under the rubric of protocol review; to communicate these policies to investigators; to administer the policies they have promulgated through the prior appraisal of research proposals, the supervision of the attempt to obtain consent and the continuing review of approved research activities; to review the consequences of their decisions; and to keep informed of DHEW policy changes and suggestions in order to reformulate institutional policies and rules when necessary.

In recognition of the variety of tasks which have been delegated to committees, DHEW policy stresses the composition of committee membership.

> . . . In addition to possessing the professional competence to review specific activities, the committee should be able to determine acceptability of the proposal in terms of institutional commitments and regulations, *applicable law, standards of professional conduct and practice, and community attitudes.* The committee *may* therefore need to include persons whose primary concerns lie in these areas rather than in the conduct of research, development, and service programs of the types supported by DHEW (emphasis supplied).[81]

In carrying out their functions, the institutional review committees are thus also asked: "to determine acceptability of the proposal in terms of. . . applicable

78. *Institutional Guide, supra,* footnote 23, at 8.

79. *Institutional Guide, supra,* footnote 23, at 8-9.

80. Although the parent institutions are charged by DHEW with the responsibility of formulating policies to guide institutional review committees, *Grants Administration Manual, supra,* footnote 23, §1-40-40, to our knowledge this task is generally delegated to those committees. As we have previously described, the burden of formulating policy weighs heavily on local institutions because the DHEW policy is vague and incomplete.

81. *Grants Administration Manual, supra,* footnote 23, §1-40-40 (C) (2) (b).

law, standards of professional conduct and practice, and community attitude." By assigning these tasks to a broadened committee membership, DHEW recognizes that decision-making in the human experimentation process cannot be left solely to professionals, but requires the participation of informed and concerned non-scientists. who may be laymen, lawyers, clergymen, and appropriate others. However, the functions of these non-professional participants are not spelled out. And the assumption that they can make their most effective contribution at the administrative stage, when individual protocols are reviewed, rather than at other stages of the process remains unexamined. The DHEW policies attempt to consolidate all phases of research regulation—formulation of detailed policies, administration of research, and review of decisions and consequences—in one committee structure. Asking each review committee to determine far-reaching policies by itself overburdens the review committee structure. The policy issues which must be resolved with the assistance of lay members are so complex that to require *each* committee to work them out by itself is at best inefficient and at worst self-defeating.

It would be more functional and efficient to leave the administration of research, like the administration of therapeutic interactions between physicians and patients, primarily in the hands of the professionals. If review committees were guided by comprehensive policies formulated by a broadly representative body, the review of individual protocols could focus on technical matters, such as degree of risk, likely benefits, research design, competence of investigators, safety precautions, and the like. This allocation of authority would help to reduce the widespread concern among physician-investigators about "meddlesome outsiders."

F. Enforcement

The DHEW guidelines on enforcement are written in permissive and general language:

> The Division of Research Grants (DRG), NIH, will follow up reports by reviewers, evaluators, consultants, and staff of the DHEW indicating concern for the welfare of subjects involved in approved and funded grants or contracts, and of subjects potentially involved in activities approved but not funded, and in disapproved proposals. On the basis of these reports and of other sources of information, the DRG, NIH, may, in collaboration with the operating agency concerned, correspond with or visit institutions to discuss correction of any apparent deficiencies in its implementation of the procedures described in its institutional assurance.
>
> If, in the judgment of the Secretary, an institution has failed in a material manner to comply with the terms of this policy with respect to a particular DHEW grant or contract, he may require that it be terminated in the manner provided for in applicable grant or procurement regulations. The institution shall be promptly notified of such finding and of the reason therefor.
>
> If, in the judgment of the Secretary, an institution fails to discharge its responsibilities for the protection of the rights and welfare of the individuals in its care, whether or not DHEW funds are involved, he may question whether the institution and the individuals concerned should remain eligible to receive future DHEW funds for activities involving human subjects. The institution and individuals concerned shall be promptly notified of this finding and of the reasons therefor.[82]

These enforcement guidelines delegate sole responsibility for the detection of failures to comply to the Division of Research Grants. But staff members of the DRG are probably the last persons to hear of any infractions once they have occurred, and then only when, as in the Tuskegee Study, they are of major proportions. Indeed, no procedures have been established to require institutional review committees to report to DHEW any evidence on noncompliance. Moreover, DHEW has made no efforts to define categories of noncompliance[83] which should lead to the imposition of sanctions or to specify different kinds of sanctions which should be imposed in particular cases. Finally, institutional review committees and DHEW are not authorized to take disciplinary action, except for the Secretary's prerogative to terminate grants or make the investigator or his institution ineligible to receive future funds.

G. Compensation of Subjects

Existing DHEW policy provides no mechanism for the compensation of subjects harmed as a consequence of their participation in research, in spite of the growing recognition that no matter how careful investigators may be, harm still will befall some subjects.[84] Unavoidable injury to a few is the "cost" of engaging in research which ultimately benefits the many. But unless the injured individuals can prove carelessness, failure to

82. *Grants Administration Manual, supra,* footnote 23, ¶1-40-50 (E).

83. Because the requirement of "continuing review" has not been elaborated, committees themselves only haphazardly come across evidence of noncompliance.

84. See Ladimer, "Protection and Compensation for Injury in Human Studies," *In Experimentation With Human Subjects* (Paul A. Freund, ed.) 247. (George Braziller, 1970) (hereinafter *Ladimer).*

obtain informed consent, or actual malice, their participation bars recovery for the harm done to them. Those subjects whose injury does result from negligence are faced with the usual difficulties and uncertainties inherent in a law suit. For his part, any investigator who is sued as a result of his research may find that his ordinary malpractice insurance does not cover medical research.[85] If it does not—and the question is as yet unsettled—the personal liability of the investigator can be substantial. In addition, the economic vulnerability of subject and investigator adds to society's uneasiness about human experimentation, and may deter some persons from engaging in research activities.

H. Applicability of DHEW Policies

The DHEW guidelines quite appropriately were formulated for research grants and contracts to be funded by the Department. While much research in this country is supported by DHEW funds, a great deal of research is also funded or conducted by other Federal agencies, such as the Department of Defense.[86] Additionally, many research activities receive no Federal support. Is there any justification for permitting less stringent protective controls for human experimentation supported by other governmental agencies, private foundations, or other private sources than for research conducted or supported by DHEW?[87] Since a major restructuring in existing policies is necessary, we believe that serious consideration should be given to developing, through Congressional action, rules and procedures which apply to the entire human research enterprise without reference to the source of funding. A tentative step in this direction has already been taken by DHEW. Its enforcement section provides for the discontinuation of funds to any institution which has failed "to discharge its responsibilities for the protection of the rights and welfare of the individuals in its care, *whether or not DHEW funds are involved.*"[88] If it is concluded, however, that such broad coverage is beyond the power of Congress, then Congress should at least act to bring all federally funded research within a comprehensive regulatory framework.

When this is done, the existing anomaly in the applicability of DHEW policies should be corrected. We refer to the different policies described earlier which govern intramural and extramural research. We can find no justification for differential protection of subjects on this basis. Moreover, the conduct of human research by DHEW employees and under the Department's aegis lends additional support to our call for an independent Government body to oversee all research. For to expect DHEW to scrutinize and judge its own activities as critically and strictly as it supervises outside research projects is arguably unrealistic and unnecessarily strains internal Departmental relationships.

85. See *Ladimer, supra,* footnote 84 at 251.

86. For documentation of the human research conducted by the armed services, see the Legislative Reference Service's report "Medical Experimentation on Human Beings, March 1967," placed in the Congressional Record by Senator Jacob Javits, 118 Cong. Rec. S. 13789, 13793-95 (August 17, 1972). The report states:

> There is very little information available on the number and types of military persons who serve as subjects in research. Intuitively appraised, however, the number of topics and of human subjects must be large.

118 Cong. Rec. S. 13793.

87. Barber *et al.,* found that in 15% of the institutions they surveyed some clinical research was not reviewed by an institutional committee. Moreover, 35% of these institutions were medical schools, "the type of institutional setting most productive of biomedical investigations using human subjects." They concluded that "a perhaps significant volume of human research is still not subject to review by peer review committees." *Barber et al., supra,* footnote 3, at 149.

88. *Grants Administration Manual, supra,* footnote 23, § 1-40-50 (E).

V. RECOMMENDATIONS

A. Preface

Before turning to our specific recommendations we would like to anticipate three possible criticisms of our proposals. First, the argument may be advanced that any regulation of human research is an unwarranted infringement of the "freedom of inquiry." But freedom of inquiry is only one facet of freedom in general. When scientists use other human beings as subjects of experimentation and in so doing jeopardize their rights and welfare, the scientists' freedom of inquiry clashes head-on with the right of every individual in our society to personal autonomy. Therefore, society must retain the right to define and limit the human costs it is willing to bear in order to benefit from advances of knowledge.

Second, whenever it is suggested that representatives of society at large participate in decision-making of significance to both science and society, concerns about the intrusion of "outsiders" in the domain of professionals are voiced. This position was forcefully expressed by Dr. Owen W. Wangensteen in a letter to Senator Walter F. Mondale prior to congressional hearings in 1968 on a proposed Commission to study the social and ethical problems raised by biomedical advances.

> Senator, I would urge you with all the strength I can muster to leave this subject to the conscionable people in the profession who are struggling valiantly to advance medicine. We are living through an era in which the innovator is often under suspicion, being second-guessed by self-appointed arbiters more versed in the art of criticism than in the subject under scrutiny. We need to take great care lest the wells of creativity and the spring of the mind of those who break with tradition are not manacled by well-intentioned but meddlesome intruders.
>
> I would urge you to leave these matters in the hand of their proponents, the persons who are actually doing the work. They know more about all this than any of us possibly could. They have wrestled with the problem day and night, almost invariably over many years. Theirs are not overnight judgments or convictions. In the academic community in which I have worked and spent my entire professional life of almost 50 years, you will find as warm, symphathetic human beings as are to be found on this earth. . . .
>
> It is important that we look back as well as forward. To have no concern for history is tantamount to having a physician with total amnesia. If we leave this matter alone, it will simmer down. Discussion should not be restrained, but legislative action, never.[89]

We appreciate Dr. Wangensteen's fears, which have been echoed by others. But not all intrusions by "outsiders" into medical decision-making are viewed by the profession as unwarranted interferences with the practice of medicine. Authorized representatives of society have the right to circumscribe some activities of professionals and this has been accepted; for example, the discretion of physicians to commit patients against their will or to prescribe addictive drugs is limited. Thus, the pertinent questions are: under what circumstances, to what extent, and by what means should the activities of the medical professional be controlled?

We have already mentioned that the human research decision-making process can be divided into three functionally distinct stages: the *formulation* of research policies, the *administration* of research, and the *review* of research decisions and their consequences. The participation of "outsiders"—which is to say, of persons deemed capable of representing the interests of society in the proper conduct of research—is highly desirable in the formulation and review stages. Such decisions as the allocation of resources for research, the extent of hazardous experimentation, the degree of respect to be shown for the autonomy of research subjects, and the extent of the participation of children, prisoners, members of minority groups, and other captive or disadvantaged persons in research, are of momentous consequence to society as well as to science. These decisions implicate general social policies and must not be left to the sole discretion of scientists.

Nonetheless, we agree that the often expressed fear of interference by laymen with the immediate clinical research decisions which physician-investigators must make has merit. However, we believe that the two positions can be reconciled. Once satisfactory rules and procedures for the protection of human subjects have been formulated and research practices are adequately reviewed by "insiders" and "outsiders," society should feel safe in leaving the actual administration of research and therapy to physician-investigators within the restraints imposed by peer review (through the already established institutional review committees.)

Current DHEW policies fail to identify the different stages in the regulation of research. Instead, institutional review committees are charged with formulating policies, administering policies, and evaluating the consequences of their decisions. Taken together these tasks are too burdensome for such committees. Moreover, because

89 *Hearings on S. J. Res. 145 before the Subcommittee on Government Research of the Senate Committee on Government Operations,* 90th Cong., 2d Sess. 98-99 (1968).

these committees must formulate policy and evaluate decisions, the demand for outsiders to sit on them has intensified, justifying the fear of interference in professional day-to-day decision-making by persons not qualified to do so. Our recommendations seek to reverse this development by confining the role of the institutional committees largely to the implementation of policies already adequately formulated by others.

A third criticism may be leveled against our recommendation that a National Human Investigation Board be established to oversee human experimentation. Some may fear that this Board will promulgate such detailed rules and impose so many legal duties that progress in research and innovation in treatment will be seriously impaired. The danger of cumbersome bureaucracy cannot be lightly dismissed and every effort must be made to avert it.[90] At the same time we doubt that society, if properly informed, would tolerate any serious impediments to the acquisition of knowledge, for the pervasive and compelling desire to benefit from advances in medicine should counteract any tendency to stifle research.

A national Board to regulate human research is needed for many reasons. One central group should be responsible for formulating policy, instead of the many different Federal agencies and the hundreds of individual review committees which, as we have argued, cannot be expected to assume this complex task. Moreover, "outsiders" who could represent and protect individual and societal values and interests could then be included in policy formulation and review, where they are most needed, without thereby hindering physician-investigators in their professional decision-making. The national Board would provide a forum in which the competing interests of science and society could be debated openly before authoritative decisions are made.

B. National Human Investigation Board

A permanent Governmental agency, to be called the National Human Investigation Board (NHIB), should be established to oversee *at a minimum* all Federally-supported research involving human subjects. The jurisdiction of this Board should extend to all extramural and intramural research sponsored by DHEW (including human research currently governed by FDA regulations) as well as to research supported by Government agencies other than DHEW, such as the Department of Defense. Ideally, the authority of this Board should also extend to all human research activities, even if not Federally supported. However, despite its apparent merits, such a sweeping proposal may raise insurmountable jurisdictional problems. We leave it to others to determine whether Congressional authority to regulate research may encompass investigations not conducted or financed by the Federal Government.[91]

The primary function of the NHIB would be to formulate policies and procedures to govern research with human beings. For this reason the Board must include, in addition to eminent medical and other professional researchers, lay members who can represent the interests of society in the ethical conduct of research with human subjects. Such lay members should be selected for their ability to make disinterested judgments about research issues of societal concern. Because medical and other research professionals have been trained to pursue other goals, they should not be expected to shoulder the added burden of speaking for the concerns of society.

Senator Hubert Humphrey has called for the establishment of a National Human Experimentation Standards Board which in some respects resembles the Board we propose. His bill[92] provides as follows:

> Sec. 2. (a) There is hereby established, as an independent agency in the executive branch, a National Human Experimentation Standards Board (hereinafter referred to as the "Board").
>
> (b) The Board shall be composed of 5 members to be appointed by the President by and with the advice and consent of the Senate from among individuals who by virtue of their service, experience, or education are especially qualified to serve on the Board. . . .
>
> * * *
>
> (3d) Members should be chosen from persons who are representative of the fields associated and concerned with clinical investigations.
>
> * * *
>
> Sec. 5. (a) It shall be the function of the Board to—
>
> (1) establish guidelines for the involvement of human beings in medical experiments which are funded in whole or in part with Federal funds;
>
> (2) review all planned medical experiments that involve human beings which are funded in whole

90. Another commonly expressed fear is that detailed regulations may adversely affect the well-being of patient-subjects because the physician-investigator's authority to intervene quickly, whenever his professional judgment dictates it, is unduly restricted. But discretionary authority must of course be delegated to physician-investigators in the exercise of purely professional judgments regarding their patient's health.

91. Senator Jacob Javits has also recently introduced a bill, in response to the Tuskegee Study, for the protection of research subjects. S. 3935, 92d Cong., 2d Sess. However, this proposed amendment to the Public Health Service Act is in essence simply a statutory enactment of current DHEW regulations. As we have argued, more than this is needed for the protection of research subjects.

92. S. 3951, 92d Cong., 2d Sess.

or in part with Federal funds to determine if the guidelines established under paragraph (1) are being complied with;

(3) obtain an injunction to prevent such experimentation in a case where such experiments are found not to comply with established guidelines; and

(4) prepare and submit an annual report to the President, for transmittal to the Congress recommending legislation, if required, and detailing the performance of the Board during the preceding year.

Senator Humphrey's bill assigns to his Board policy making, administrative and review powers. We believe that some of these functions should not be delegated entirely to the NHIB and that those functions which the NHIB should be given must be spelled out in greater detail. Senator Humphrey's bill also does not provide for the continuation of the institutional review committee system. We believe that institutional review committees should be maintained, although in modified form. We now turn to a discussion of the functions of the NHIB and institutional committees in the formulation, administration and review of policies for human research.

1. Formulation of Policy

The National Human Investigation Board must establish guidelines for the conduct of research with human beings with respect to such matters as:

a. *Selection of Subjects*—The Board must formulate criteria for the selection of subjects. It will have to reexamine the contemporary research practice of choosing subjects from the less educated, disadvantaged, or captive groups within society. In doing so, the Board will have to confront many questions. For example, should every effort be made, consistent with research objectives, to obtain a subject sample which represents a cross-section of the population at large? Or should subjects first be selected from among the best educated before turning to the less educated, since the former are more capable of giving "informed consent"? How should the recruitment of subjects be effectuated to implement whatever rules for their selection are adopted? Under what circumstances should non-comprehending subjects such as children or severely mentally disturbed individuals, or captive subjects such as prisoners or other institutionalized persons, be barred from participating in research?

b. *Ambit of Informed Consent*—The Board must not only formulate the overall criteria of informed consent but must also specify the circumstances in which the consent requirement can be modified, and to what extent, in order to accomplish important research objectives. In doing so, the Board will have to find answers to such policy questions as: Under what circumstances can what benefits to individuals or society justify modifications in the informed consent requirement? Should certain groups or potential subjects be excluded from participating in research or high-risk investigations be proscribed unless informed consent can be obtained? When is third party consent permissible, and what safeguards should be introduced whenever the consent of a third party is invoked? The Board may have to promulgate separate guidelines for the conduct of investigations which are predicated on the absence of informed consent, such as placebo, double blind, deception and secret observation studies. The latter two procedures are employed by sociologists and psychologists on such an extensive and repetitive scale, and constitute such a significant exception to the general requirement of informed consent, that serious consideration should be given to restricting their use.

This may be an appropriate place to introduce a note of caution. The policies we have in mind cannot be formulated overnight or without serious study of the problems inherent in this field. An example from the literature on informed consent illustrates this point. It has traditionally been assumed that the consent requirements should be more stringent in research with "healthy" volunteers than with patients. This assumption ought to be reexamined. Perhaps, as Alexander Capron has written:

> . . . higher requirements for informed consent should be imposed in therapy than in investigation, particularly when an element of honest experimentation is joined with the therapy. The "normal volunteer" solicited for an experiment is in a good position to consider the physical, psychological and monetary risks and benefits to him in consenting to participate. How much harder that is for the patient to whom an experimental technique is offered during a course of treatment. The man proposing the experiment is one to whom the patient may be deeply indebted (emotionally as well as financially) for past care and on whom he is probably dependent for his future well-being; the procedure may be offered, despite its unknown qualities, because more conventional modalities have proved ineffective.[93]

Finally, more attention must be given to the nature

93. Capron, "The Law of Genetic Therapy," in *The New Genetics and the Future of Man*, M. Hamilton, ed. (Eerdmans Pub. Co., 1972).

and quality of the interactions between investigator and subject if the ensuing consent is to be truly informed and voluntary. In this connection, consideration should also be given to make an adviser available to a subject whenever he thinks that his decision to participate or not might benefit from disinterested advice.[94] The authority and obligations of such advisers must be carefully defined and, as we have said repeatedly, with regard to policy formulation, cannot be left to each individual research committee to work out.

c. *Definition of "Research"*—To clarify the jurisdiction of the Board and of the institutional review committees, distinctions must be made between "research" activities and "accepted and established procedure." We have pointed out already that the borderline between research and therapy is difficult to draw. Physician-investigators have often wittingly or unwittingly added to the obfuscation by calling some investigations "therapy." in order to escape the obligations which the research designation entails. Such practices diminish the protection afforded subjects, and also undermine the scientific validity of the results of such investigations, because they were not established in carefully controlled clinical trails.

d. *Application of Risk-Benefit Criteria*—We have already suggested that the risk-benefit equation is one of the most difficult guidelines to implement. To evaluate risk taking, distinctions must be made between research designed to benefit its participants and those which may benefit society at large. With respect to societal benefits, answers will have to be found to such crucial questions as: Do even minimal risks from participation require an intensive scrutiny of the benefits to be derived from the study or should "minimal" risks, however defined, be exempted from this burdensome requirement? How often can risky experiments be repeated for the sake of verification, if results have already been reported in the literature? Must certain groups, such as children and mentally defective subjects, be excluded from all risky studies that are not designed to benefit them? When the risks and benefits of therapeutic measures are unknown, as in all first clinical trials of a new drug, should the tests be randomized with a limited number of patients in order to ascertain a scientifically valid estimate of effectiveness? In research with so-called normal volunteers or other subjects who are able to give a satisfactory consent, can greater risks to be taken than a weighing of risks against benefits would in general permit? Should dying patients who are willing to participate in risky experiments be exempted from the rule that no experiments are to be conducted which might hasten death?

e. *Promulgation of a Compensation Scheme*—An insurance plan should be devised and implemented for the compensation of subjects harmed as a consequence of their participation in research activities. Though many schemes for compensating subject deserve consideration, we mention one which we believe has substantial merit: "no fault" clinical research insurance paid for by each institution sponsoring research. Subjects would be compensated for any injurious consequences of their participation in research whether or not caused by the fault of the investigator. This plan would provide full protection for subjects and relieve investigators of the threat of liability. As to cost, one of the principal promoters of research insurance, Irving Ladimer, has asserted that:

> . . . it is unlikely that the costs will be great, probably a small fraction of customary malpractice premiums. First, there are few compensable occurrences within responsible research institutions, where most of the studies are conducted. Second, the assumption of medical care, most likely at the sponsor's premises, will reduce such costs. Third, the adoption of such a system should tend to improve prior protection, controls, and research design; this is expecially true for studies approved by research review committees. Fourth, the spirit and philosophy of this form, which should be fully explained in advance in discussions with participants, should serve to diminish rather than induce any questionable claims.[95]

The cost of the insurance would probably vary directly with institutional safety records and thus might provide an additional impetus to careful consideration of research proposals. Guido Calabresi has called attention to this possiblity:

> . . . Requiring compensation of injured subjects causes the full cost of research in humans to be placed on the research center. Accordingly, approval by the center of a particular experiment will require conscious consideration not only of the possible payoff (either in market or scientific terms), but also of the risks, converted to money, that the project entails. This may not deter many experiments, but it may cause those involved in the most risky or least useful ones to consider carefully whether the experiment is worth it, whether it is best done by those who propose to do it, and whether there is an alternative, and safer, way of obtaining approximately the same results. It may well be that all these considerations are already firmly in the minds of the experi-

94. We elaborate upon this recommendation *infra*, pp. 44 ff.

95. *Ladimer, supra*, footnote 84, at 259.

menters. If so, nothing is changed by requiring compensation. But if researchers–like auto makers, coal mine owners and the rest of mankind–tend to consider costs and benefits a bit more carefully when money is involved, a useful added control device will have been imposed.[96]

If "no fault" research insurance, or any other mechanism, is adopted as a device for compensating subjects, regulations will have to be established for adjudicating disputes over such matters as causation–whether the worsened condition of the subject was caused by the research in which he participated or whether it was merely the inevitable outcome of the subject's particular illness–or the amount of compensation. Similarly, the NHIB will have to work out procedures for implementing whatever compensation scheme is adopted.

f. *Promulgation of Sanctions*–Senator Humphrey's bill authorized his Board "to obtain an injunction to prevent. . .experimentation in a case where. . .experiments are found not to comply with established guidelines." Though the promulgation of sanctions raises many sensitive issues, more is needed than has been provided in Senator Humphrey's bill. Other sanctions tailored to specific violations of the policies governing research are required. For example, an investigator's failure to submit a protocol for review, his departure from an approved research protocol or a review committee's failure to follow its established procedures might in some circumstances justify suspension of further Federal funding of the investigator or the sponsoring institution.

It is beyond the scope of this report to detail the offenses which should lead to the invocation of sanctions, the particular penalties which should be imposed, or the procedures which must be followed to satisfy due process requirements. We also leave open the question of who–the National Human Investigation Board or Congress–should promulgate the regulations which will govern the imposition of sanctions.

g. *Delegation of Authority to Administer and Review the Research Process*–The National Human Investigation Board must also promulgate rules and procedures for the administration and review of the human research process. We now turn to these issues under their appropriate headings.

2. Administration of Research

a. Institutional Human Investigation Committees

Once adequate research policies have been formulated by a broadly representative body, "outsiders" should intervene as little as possible in the administration of those policies. For when research policies are put into effect, limitations imposed by colleagues are better tolerated by investigators than restrictions imposed by outsiders. The administration of research should therefore be performed principally by researchers' professional peers sitting on institutional review committees. Thus we seek to reverse the trend[97] toward outsider membership on institutional review committees and outsider interference with day-to-day professional decision-making. In our proposed restructuring of institutional review committees, we have sought to restrict the participation or outsiders to those areas where they have the most to contribute.

Senator Humphrey's bill does not specify the status of the institutional review committees which are now required by DHEW. The advantages of institutional committees are numerous, and we propose that they be retained, though with redefined functions. Among other things, administration at the institutional level simplifies the task of prior review of research protocols; permits closer scrutiny of research activities; encourages investigator involvement in and respect for the problems of ethical research; enables different institutions to deal with complex new problems from different vantage points, and facilitates responsiveness to difficulties in the research process as they arise. Instead of eliminating institutional committees, they should be restructured to enable them to perform their functions better than they now do.

We recommend the creation of a structured institutional body, to be called the Institutional Human Investigation Committee (IHIC), in place of the existing unspecialized institutional review committee. Each institution which is subject to the jurisdiction of the NHIB would be required to provide written assurance to the NHIB that it had appointed an IHIC. This would be similar to current practice which requires institutions to negotiate assurances with the NIH's Division of Research Grants.[98] As outlined below, each IHIC would be responsible for the conduct of research in its institution, and would be required to file with the NHIB its plans for carrying out the responsibility. Thus the NHIB would pass on the suitability of the IHIC membership, local policies, and administrative procedures, and NHIB

96. Calabresi, "Reflections on Medical Experimentation in Humans," 98 *Daedalus* 387, 398 (1969).

97. Current DHEW regulations suggest, and FDA regulations require, that outsiders be members of institutional review committees. See *Grants Administration Manual, supra,* footnote 23, §1-40-40 (C) (2) (b); 21 CFR §130.3; 36 Fed. Reg. 5037, 5038 (March 17, 1971).

98. See *Grants Administration Manual, supra,* footnote 23, §1-40-40 (A):

> The assurance shall embody a statement of compliance with DHEW requirements for initial and continuing committee review of the supported activities; a set of implementing guidelines, including identification of the committee; and a description of its review procedures. . .

approval would be required before Federally funded research[99] could be conducted at the institution.[100]

IHIC members should be appointed by their institutions to serve for a period of years, so as to accumulate expertise in the problems of human experimentation. The membership should represent a cross-section of the disciplines involved in research at the institution. It ought also to include a few "outsiders." who can make a valuable contribution to the supervision of the consent process, as described below.

The main functions of each IHIC would be: to establish local policies, consistent with the uniform national guidelines promulgated by the NHIB, which are responsive to the individualized needs of the institution, to bring to the attention of the NHIB any procedural modifications deemed necessary for effective functioning; to inform local participants in the research enterprise of their rights and obligations; and to establish two subcommittees to carry out its administrative functions—a Protocol Review Group and a Subject Advisory Group. Although the membership of the subcommittees should be drawn largely from the IHIC, these subcommittees could also include others associated with the institution. Our recommendations regarding the two subcommittees are modeled on a similar proposal recently advanced by Jay Katz and Alexander Capron in a somewhat different context, and in what follows we quote from the draft document they have prepared.

b. Protocol Review Groups

> The heart of IHIC's will be their Protocol Review Groups (PRG) which will be responsible for approving, disapproving or offering suggestions for modification in protocols for experimental and therapeutic interventions which come within the policies on risk and consent formulated earlier in the process. The PRG's task is to apply the rules and policies already set down, but this should not be a matter of "clockwork" or mere routine. Realistically, it is unlikely that even if policy formulation proceeded with much more rigor (as we urge) it will result in directive that settle all issues faced by the PRG's. This does not suggest, however, that Protocol Review Groups set policies themselves, though these rules may give them some discretion in light of local institutional conditions and so as to permit experimentation with a variety of alternative policies which are still consistent with the general directives. This sort of flexibility is vital if the PRG's are to operate effectively and secure the services of thoughtful, devoted members.
>
> Membership in the Protocol Review Group should consist primarily of professionals with competence in biomedicine. This reflects the committee's function, which is to scrutinize protocols in light of the policy guidelines and directives, to evaluate whether the procedure should be undertaken, and to give advice to the physicians and scientists involved. In most instances these group members will be members of the university or research center's staff and faculty, but when the presence of more than one institution in a locality permits it, the cross-fertilization of having some people from one center serve on another's PRG would probably be advisable. Such an arrangement would provide "outsiders" in the sense of people's free of the personal ties and biases of the institution's own employees, while maintaining the biomedical expertise that should characterize "insiders."[101]

c. Subject Advisory Groups

Katz and Capron also propose "the establishment of Subject Advisory Groups (SAG) to aid patient-subjects in decision-making."[102] We do not lightly suggest the creation of another subgroup within the IHIC, since we have no desire to overburden the process with excessive bureaucracy. But, as we have emphasized, present procedures for obtaining consent are concerned with form to the neglect of substance. If informed and voluntary subject consent is to become a reality in human experimentation, efforts must focus on improving the quality of the communications between investigator and subject. We therefore endorse the Katz and Capron proposal that an adviser be made available to counsel any prospective subject who thinks his decision to participate or not might benefit from disinterested advice.

> Not all patient-subjects may wish to seek out representatives of the Subject Advisory Group, for some may be satisfied with the information obtained from physician-investigators. But patient-subjects should be well apprised of the availability of these representatives prior to their participation in projects which have to be sub-

99. Or any research — see *supra*, p. 39.

100. It should be noted that, as in present DHEW policy, different requirements might be established for institutions "having a significant number of concurrent" research projects and for institutions sponsoring only one, or a limited number, of such projects. See *Grants Administration Manual, supra*, footnote 23, § 1-40-40 (B), (C), and (D). The description of the IHIC presented in our report hereinafter is for an institution with a number of research activities.

101. *Katz and Capron, supra*, footnote 18.

102. *Ibid.*

mitted to the PRG because of the risk involved or because of the problems anticipated with obtaining valid consent. Patient-subjects may also wish to avail themselves of the SAG's services when they begin to wonder whether continuation of the intervention is worth the pain and suffering they have to endure. At such times the Subject Advisory Group assumes the important function of administering the procedures formulated for the termination of experimental treatments.[103]

The SAG should also aid investigators in developing fair methods of obtaining consent, and in avoiding inadvertent bias or coercion when seeking consent. It ought to go without saying that

> . . . (c)reating an opportunity for someone in addition to physician-investigators to talk with patient-subjects does not suggest a lack of trust in the investigators' integrity, rather it recognizes the reality that investigators cannot help but plead, however unconsciously, their interests in the research and therefore must find it difficult fully to safeguard the interests of their subjects.[104]

Because the work of the SAG would be restricted to issues relating to consent, laymen could make a significant contribution in this subcommittee. They, more than professionals, would appreciate the difficulties prospective subjects might have when faced with an invitation to participate in research. And potential subjects might be less overawed in interactions with their peers, than in interactions with physicians.

d. Appeals

From time to time disagreements will arise between investigators and the Protocol Review Groups. No opportunity for appeal from an adverse institutional review committee ruling exists at present, and committees can cut investigators off from Federal funding without possibility of reconsideration. This may not only hinder the acquisition of knowledge; it may also undermine the legitimacy of peer review. Barber *et al.* have written:

> We have heard researchers object to peer review as they know or understand it because they believe that research proposals having real potential for medical scientific advances, or even "pioneering breakthroughs," frequently either are not or will not be approved by those who sit on institutional review committees. The reasons for these rejections they are especially concerned about do not involve the ethical defectiveness of the proposals. Rather they include local institutional politics and conflicts as well as resistance to innovations just because they depart from accustomed ways of scientific thinking and proceeding. . . (T)o forestall rejections of this kind, the biomedical community may have to go beyond the establishment of local appeal procedures by institutions. Perhaps what is necessary is the establishment of a hierarchy of "courts of appeal" thoughout the nation, culminating, as a final resort, in a "supreme court" composed of eminent peers including both "insiders" and "outsiders" with respect to any field. Such a system might be the best safeguard available against the object of these concerns—unjustified hindrance of medical progress by the peer review process.[105]

Procedures should be established for appeals to the National Human Investigation Board.[106] After a hearing of the controversy, the NHIB should be empowered to sustain or overrule the judgment of the Protocol Review Group.

Since the NHIB has a role to play in the administration of research, it must employ expert staff to evaluate research protocols and to prepare detailed findings. This staff would take over the reviewing function currently handled by DHEW study groups. However, it is beyond the scope of this report to set forth all the specific functions which the NHIB should assume. In particular, we have refrained from deciding how many of the protocols approved by the PRG's should be reviewed again by the NHIB. Though a certain number will have to be examined in order to provide the NHIB with sufficient information to carry out its most important function—policy formulation,—it may not be necessary to review all protocols a second time. This would be a time-consuming task.

3. Review of Decisions and Consequences

The NHIB must create mechanisms for the overall review of the human experimentation process in order to assess the continuing efficacy of its own policies and of the institutional peer group review. Thus, the Board has to keep itself informed about ongoing research practices, and a number of already esisting resources would facilities this task: scientific journals which publish research studies, legal cases in which conflicting claims about research have been brought before courts, newspaper accounts (such as the initial reports of the

103. *Ibid.*
104. *Ibid.*

105. *Barber et al., supra,* footnote 3, at 156-157. (footnote omitted).

106. IHIC's might also find it appropriate to establish an internal appeals procedure. This would be more convenient than, and would sometimes obviate the need for, appeals to the national level.

Tuskegee Syphilis Study), reports from Institutional Human Investigation Committees, etc.[107]

The NHIB must also establish rules and procedures for the direct review by IHIC's and by NHIB staff members of ongoing previously approved research projects. The current requirement of systematic review of all projects at fixed intervals is burdensome and inefficient and encourages perfunctory review. Instead of requiring continuing review of all research projects on a routine basis, it would reduce the burden on IHIC's and maximize the effectiveness of continuing review if investigators were asked to report immediately any contemplated or necessary deviations from approved research protocols, all inconveniences and injuries suffered by any subjects which has not been anticipated in the original protocol, or any medical advances which might benefit subjects and which has not been anticipated in the original protocol. Moreover, periodic "spot checks" of selected interventions which are now discretionary should be made a requirement. It is apparent that some approved research projects are carried out improperly. For example, in a recent study involving subjects subsequent to their participation in a medical research project which had been approved by an institutional review committee, an interviewer found that,

> (m)ost of these subjects learned of the existence of the study during the interviews done for my research. Second, many more subjects (the exact number awaits further analysis), while aware of the research, has significant gaps in their understanding of the project and consented on a more or less uninformed basis. These included women who had no knowledge of whether there were alternatives to participation, women who did not know of the double-blind nature of the study (it was not part of the research design to withhold this information), and women who were not aware of the fetal monitoring procedures and extra blood samples required by the research. Others were not aware beforehand that their consent to have the baby observed would be sought by a separate researcher.[108]

Spot checks would determine the extent of noncompliance with existing procedures. Should the checks reveal widespread noncompliance, then remedial steps could be taken, such as better education of physician-investigators about their responsibilities, more careful evaluation of protocols, or routine monitoring of all research activities for a period of time.

The NHIB should also invite the IHIC's to submit their most difficult decisions for an evaluation. Significant cases, inclucing the original PRG rulings and the subsequent NHIB opinions, should be published to give direction to the deliberation of local committees, to provide material for scholarly analysis, and to foster and sustain public awareness of the issues raised by human experimentation. Indeed, all important decisions rendered at the local or national level should be published and preserved in easily accessible form. These cases would serve as precedents for future opinions. Thus publication would be a first step toward the case-by-case development of sound policies for human experimentation. We regard such a development, analogous to the growth of the common law, as the best hope for ultimately providing workable standards for the regulation of the human experimentation process.

Finally, we emphasize again that the review of research decisions and their consequences requires the participation of persons representing a wide variety of societal interest and should not be limited to members of the biomedical professions. It is at the policy-formulation and review stages of the human experimentation process that "outsiders" have an important role to play by championing individual and societal rights and interests. Professionals have been trained to pursue other goals and should not be expected, even if they could, to shoulder the added burden of speaking for the concerns of society.

C. Education

Our last recommendation pertains to the education of investigators, particularly when they are still students, for the responsible practice of human research in a democratic society. Recently, Senator Jacob Javits introduced a bill[109] in the Senate which addresses itself to this problem. The bill

> would authorize special project grants for medical schools to develop and operate programs which provide increased emphasis on the ethical, social, moral, and legal implications of advances in biomedical research and technology.

* * *

107. The NHIB might consider inviting others – for example, editors of scientific journals – to submit for review studies which raise ethical questions. Editorial boards should welcome such an opportunity, particularly in the light of the recent debate about the publication of articles based on "unethical" research. Some commentators have favored non-publication, while others have felt that "(s)uch an editorial policy would maintain the low visibility of unethical experimentation and preclude not only review but also careful and constant appraisal of the conflicting values inherent in experimentation." (Katz, "Human Experimentation," 275 New Eng. J. of Med. 790 (1966)). Journal censorship creates difficult problems. If editorial boards could be assured that violations of "ethical" practice would be dealt with by an authorized body, they might prefer to call them to the attention of the NHIB and judge acceptability of articles on the basis of scientific merits.

108. Gray, "Some Vagaries of Consent," a preliminary report (1971) on data collected for the author's doctoral thesis, reproduced in *Katz, supra,* footnote 12, at 660.

109. S. 974, 93d Cong., 1st Sess.

> The bill... provides the opportunity for our Nation's medical schools to develop the appropriate program curriculums regarding ethical, moral, and social issues to meet the need–the protection of human subjects at risk in medical research and improved understanding of the consequences and implications for the individual and society of the advances in biomedical science–and through their own initiative and leadership construct and appropriate continuing professional institutional activity to safeguard human subjects in research.[110]

Senator Javits referred to the findings of Professor Bernard Barber *et al.*, and to document further the need for such an educational effort, we quote briefly another passage from their study:

> It is clear from our date that medical schools are presently giving very little serious attention to these matters in their curriculum. Of the 307 physicians interviewed, only 13% reported that they had had a seminar, a lecture or part of a course devoted to the issues involved in the use of human subjects in biomedical research, and only one researcher said that he had had a complete course dealing with these issues. Thirteen per cent of the respondents said that the issues of research ethics came up when as students they did practice procedures on one another, and 24% said that they became aware of the issues of balancing risk or suffering against potential benefits when doing experimental work with animals. Thirty-four per cent remembered discussions with instructors or other students of the ethical issues involved in specific research project which they had read about or learned of in class. But 57% of the physicians interviewed reported none of these experiences, even those peripheral to work with humans, such as those involving animal experimentation.[111]

It has sometimes been asserted that the human subject in experimentation is best safeguarded "by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator."[112] Whatever merit underlies such a contention, sufficient attention has not been paid by educators in all professional schools to exploring the responsibilities of the professional toward his patients, clients, or research subjects. Without training, even a "conscientious" investigator is poorly prepared to deal knowledgeably or systematically with these problems.

Though in recent years there has been an upsurge in efforts to expose students to the issues raised by professional responsibility, considerably more thought and support must be given to this work. Professional schools must recruit faculty members who are interested in pursuing the complex problems created by human research in particular and contemporary professional practices in general. The task is not limited to educating students but must ultimately include a re-examination of the entire scope of professional decision-making.

110. 110 Cong. Rec. S 3114 (Feb. 22, 1973)
111. *Barber et al., supra,* footnote 3, at 101;
112. Beecher, "Ethics and Clinical Research," 274 New Eng. J. Med. 1354, 1360 (1966).

VI. CONCLUSION

Human experimentation reflects the recurrent societal dilemma of reconciling respect for human rights and individual dignity with the felt needs of society to overrule individual autonomy for the common good. Throughout this report we have expressed our concern for the lack of attention which has been given to the protection of the rights and welfare of human subjects in research. Society can no longer afford to leave the balancing of individual rights against scientific progress to the scientific community alone. The revelations of the Tuskegee Syphilis Study once again dramatically confirmed this conclusion.

We offer our far-reaching proposals in the hope that the decision-making process for human research will become more open and more effectively regulated. We have amply documented the need for implementing this most basic recommendation. Precise rules and efficient procedures, however, are not by themselves proof against a repetition of Tuskegee. For, however well designed the system of regulation, the danger of token adherence to ethical standards and evasion in the guise of flexibility will persist. Ultimately, the spirit in which an aware society undertakes to use human beings for research ends will determine the protection which those human beings will receive. Therefore, we have urged throughout a greater participation by society in the decisions which affect so many human lives.

Respectfully submitted,

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