

An ad hoc committee set up in the spring to review the Head Injury Research Laboratory of the School of Medicine completed its report on August 2; it is published in this section of Almanac starting on page III. Below and on page II is the text of a separate report summarizing recent events surrounding the Laboratory. It was prepared by the Secretary of the University, Dr. Mary Ann Meyers, on August 23.

An Update on the Head Injury Laboratory

The Head Injury Clinical Research Laboratory in the School of Medicine remained in the headlines this summer as the federal government suspended its funding and President Sheldon Hackney halted its use of animals in experiments designed to determine the best treatment for human victims of trauma-caused brain damage. The president's action was taken in late July in response to concerns raised in a preliminary report by the National Institutes of Health (NIH). A week earlier Secretary of Health and Human Services Margaret M. Heckler cited the same report in ordering suspension of an annual \$1-million NIH grant for support of the baboon research project.

Secretary Heckler's order followed four days of sit-ins by animal rights activists at institute headquarters in Bethesda, Md. and was given on the basis of evidence from the laboratory gathered in a 1984 raid by the Animal Liberation Front (A.L.F.). The activists stole videotapes made by researchers to document more than 60 hours of experiments in which baboons' heads were subjected to sudden acceleration to induce brain injuries. A 24-minute edited version has been exhibited around the country by People for Ethical Treatment of Animals, and the organization claimed Secretary Heckler's decision as a major victory while scientists criticized it as an apparent capitulation to extremists.

The NIH preliminary report, which has not been publicly released, stressed that the experiments were both justified and appropriate but concluded that there had been material failure to comply with health policy for the care and use of laboratory animals. It raised questions about the management of anesthesia and analgesia, according to NIH director James B. Wyngaarden, a former member of the Medical School faculty, as well as about the supervision

and training of laboratory personnel, sterilization experiments, and the occupational health program in the Head Injury Laboratory. The report also stated that the deficiencies in the project can be corrected because they are not part of the research's basic concept or protocol or its experimental approaches.

A University ad hoc committee subsequently concurred with the NIH reviewers about the scientific merit of the head injury research. In a report issued in early August, the Penn investigators described the study as being of "great importance to human welfare," but they also found practices that were not in compliance with NIH guidelines. The infractions included smoking in the operating suite, lack of aseptic surgical techniques, casual dress, a sub-standard recovery room, incomplete post-operative records, and inadequate supervision of the animals by a qualified veterinarian.

Unlike the NIH reviewers, who questioned the effectiveness of drugs used to anesthetize the laboratory baboons on the basis of videotape records of the animals' movements and researchers' statements about alleged wakefulness, the Penn committee was satisfied that the doses of anesthesia were always fully adequate. The internal review team reached its conclusion on the basis of the stability of recorded physiological parameters as well as the nature of the baboon's movement, which were much slower than is characteristic of an unanesthetized state.

Furthermore, the University committee noted that while it does not condone "instances of apparent inappropriate jocularity and offensive comments" visible on the videotapes, it felt certain that the seemingly callous remarks of the young researchers "do not reflect the general . . . manner in which experiments were carried out." In conclusion, the Penn reviewers

declared their belief that the Head Injury Lab "has made significant changes and improvements . . . and that current protocols and facilities are in compliance" with the NIH guidelines.

Upon receiving the report, Dr. Hackney said that he was reassured by the committee's findings that the treatment of research animals met NIH standards. But he has also noted that "the lack of cleanliness in the lab, the sub-standard recovery room, the lack of adequate supervision by a veterinarian, the smoking, the inappropriate comments . . . are not acceptable at this University." According to the president, the administration "will not permit the lab to resume experiments with animals" unless both Penn and NIH officials "are fully satisfied that the use of animals in the research project is in complete compliance with all relevant guidelines and that there will be no deviations, no matter how slight, from those guidelines."

The research activities of the Head Injury Lab were suspended for three months during the winter of 1982-83 by Dean Edward J. Stemmler on the advice of the Medical School's Animal Care Committee. Subsequently the committee reviewed a tape of a procedure and interviewed investigators involved with the study. It then unanimously approved continuation of the project, and in March of 1983 the dean released the lab from research restrictions.

NIH has been supporting the head injury project at the rate of about \$1 million annually for the past 13 years. Since the 1984 break-in focused national attention on the Medical School lab, favorable assessments of the research have been made by four distinguished review groups. The current NIH and University investigations were delayed by the refusal of animal activists to provide officials with copies of the stolen videotapes until one year after the A.L.F. raid.

Within a week after receiving the NIH's preliminary report, on which the suspension of funding was based, the University submitted an interim response. It contained a report to Provost Thomas Ehrlich and Dean Stemmler from Vice President for Health Affairs Thomas W. Langfitt and Associate Professor of Neurosurgery Thomas A. Gennarelli. Dr. Langfitt is principal investigator for the Head Injury Clinical Research Center, a government-supported enterprise, which is primarily focused on research involving human victims of severe head injury. Over the past dozen years, a portion of the Center's budget has funded the laboratory project using primate models. It is directed by Dr. Gennarelli.

In their report, the Penn scientists make clear that whatever the past deficiencies in the lab, general supervision and operation of the research facility will in the future fully conform to Public Health Service guidelines. Furthermore, they deny all allegations of inhumane treatment of animals and provide a comprehensive account of the anesthetic and analgesic agents, which expert site visitors and consultants to the Medical School's Animal Care Committee have found suitable for the prevention and relief of pain.

Meanwhile, many members of the biomedical research community have expressed dismay that the government's decision to suspend support for Penn's head injury research project seemed to come in direct response to pressure from animal rights protestors. In a letter to Secretary Heckler, the Association of American Medical Colleges and three other academic organizations wrote that appearing to capitulate "to the demands of an irresponsible advocacy group . . . increases the vulnerability of academic institutions to further break-ins, destruction of property, and loss of research data of incalculable value."

But the government's focus on the Head Injury Lab continues, and in late August the Department of Agriculture is expected to file a complaint against the University charging violations of the Animals Welfare Act. The Subcommittee on Oversight and Investigations of the House Science and Technology Committee has requested information on the baboon project from NIH and may hold hearings when Congress returns after Labor Day. Reportedly, more than a dozen congressmen are sponsoring an amendment to the NIH's annual appropriations bill that would permanently cut off federal funding for the lab even if the final NIH report gives it a clean bill of health.

Washington-based trustee John H. Porter, chairman of the public relations firm of Needham, Porter & Novelli, has been advising the administration on public relations aspects of the challenge from animal rights activists. Surveying the summer's developments, he suggests that continued focus of the media spotlight on the Head Injury Lab will make Penn the standard bearer for the cause of animal research—highly visible and, therefore, an easy mark for snipers.

Report of The Committee to Review The Head Injury Clinical Research Laboratory Of the School of Medicine

TABLE OF CONTENTS

I.	Introduction	III
II.	Committee	III
III.	Pre-Meeting Activities	IV
IV.	The Review	IV
V.	History	IV-V
VI.	General Findings	VI
	a. Compliance with the Guide	
VII.	Specific Findings	VI-VIII
	1. Scientific Merit	
	a. The Magnitude and Importance of Head Injuries	
	b. The Experimental Design	
	c. The Results	
	d. Adjuncts to the Baboon Model	
	e. Peer Judgment	
	2. State of the Animals, Their Awareness to Pain and Their Care in Acute and Chronic Studies	
	a. Pre-Injury	
	b. At the Time of Injury	
	c. During the Post-Injury Period	
	d. At the Time of Sacrifice	
	3. Placement and Removal of the Helmet	
	4. Review and Monitoring of Studies	
	5. Facilities	
	6. Conduct and Demeanor of the Laboratory Personnel	
VIII.	Conclusions	VIII
IX.	Recommendations	VIII

Report of the Committee to Review The Head Injury Clinical Research Laboratory Of the School of Medicine

August 2, 1985

I. Introduction

In January of 1985, Dr. Barry S. Cooperman, Vice Provost for Research at the University of Pennsylvania, invited five members of the Medical School faculty to address allegations concerning inhumane use of baboons in research conducted by the Head Injury Clinical Research Laboratory of the University of Pennsylvania School of Medicine (Appendix I), and to give advice on the appropriate University response. In March of 1985, the five members of the Medical School faculty met with Dr. Cooperman and agreed that 1) the University should appoint a committee to conduct a thorough review of experiments carried out in the Head Injury Clinical Research Laboratory and 2) the review should be undertaken as soon as a suitable process could be put in place. It was further agreed that the review committee be drawn primarily from the faculty of the School of Medicine, but that membership should also include faculty from elsewhere in the University, biomedical faculty from outside the University and an educated layperson or persons with no University connections. Subsequently, Vice Provost Cooperman strongly urged President Hackney, Provost Ehrlich and Dean Stemmler to undertake the review (Appendix II).

On May 8, 1985, the President and Provost of the University on the advice of the Vice Provost for Research and the Dean of the Medical School appointed a nine member committee specifically charged with 1) determining whether the use of animals in research carried out in the Head Injury Clinical Research Laboratory has been and is in accordance with norms established by the National Institutes of Health governing the conduct of research on animals and 2) to make recommendations concerning use of animals in future research in the Laboratory (Appendix III).

Although the committee's deliberations were not to be recorded, the committee was charged with describing its findings and making recommendations in a written report subsequently to be made available to the public. The committee conducted its review of the Head Injury Clinical Research Laboratory on June 17-18, 1985.

The following is a description of the review process, the findings of the committee and its conclusions and recommendations concerning future animal research in the Laboratory.

II. Committee

The Committee consisted of three members of the School of Medicine faculty: Dr. Jonathan Rhoads, John Rhea Barton Professor of Surgery, and former Chairman of the Department of Surgery, 1959-1972; Dr. Arthur Asbury, Ruth Wagner Van Meter and J. Ray Van Meter Professor of Neurology and former Chairman of the Department of Neurology; and Dr. Truman G. Schnabel, C. Mahlon Kline Professor of Medicine, and Distinguished Professor of the School of Medicine; three members of the University at large: Dr. Abraham Edel, Professor of Philosophy; Dr. Daniel J. O'Kane, Professor of Biology and Associate Chairman of the Department of Biology; and Dr. Stephen P. Schiffer, Director of the Unit for Laboratory Medicine, School of Veterinary Medicine; and three lay-individuals: Rev. Frank M. Harron, Rector of St. Peter's Church in the Great Valley, Consultant in Bioethics, National Council of Churches; Mrs. Pauline Innis, Author and Public Member; and Mr. Erik Hendricks, Executive Director, Pennsylvania Society for the Prevention of Cruelty to Animals. Dr. Truman G. Schnabel assumed the chairmanship of the committee (Appendix IV).

Dr. Schnabel's membership on the committee was subsequently challenged by Dr. Gary L. Francione, Assistant Professor of Law, University of Pennsylvania, because of Dr. Schnabel's administrative support of the original NIH grant which established the Head Injury Research Center at the Philadelphia General Hospital in 1970 (Appendix V). At that time, Dr. Schnabel was Coordinator of the University of Pennsylvania Service and acted as the chief administrative officer for the University's medical service at the Philadelphia General Hospital. It was customary for him to lend support to research projects carried out by University personnel. In addition, as chief of the medical service, it was entirely appropriate to support a study of patients with head injuries. Dr. Schnabel left the Philadelphia General Hospital in 1972 and had no further knowledge of the work carried out in the Head Injury Clinical Research Unit. Dr. Schnabel remained as chairman of the committee at the request of the Provost of the University and with the consent of the other members of the committee.

Mr. Erik Hendricks' membership on the committee was also challenged by Professor Francione. He charged that Mr. Hendricks was biased as evidenced by statements alleged to have been made by Ms. Elaine Newton, an employee of the Pennsylvania S.P.C.A., in which she was quoted as saying that she and Mr. Hendricks had seen the excerpted tape and that "the tape was taken out of context and that's unfair." Mr. Hendricks remained a member of the committee with the consent of the other members.

III. Pre-Meeting Activities

The President's and Provost's letter to the committee also contained an outline of the events leading up to the committee's appointment and the following documents:

1. The standards established by the National Institutes of Health in 1978 governing the conduct of research on animals.
2. Report of the Society for Neuroscience after its review of the Head Injury Clinical Research Laboratory.
3. Minutes of the School of Medicine Animal Care Committee.
4. Documents from the University of Glasgow.
5. The recorded proceedings of the discussion held on January 15, 1985 that was led by Dr. Barry S. Cooperman and involved members of the Law School faculty, Drs. Thomas Langfitt, Thomas Gennarelli and others. These proceedings were later published in the Almanac on February 19, 1985.
6. Pertinent sections of Drs. Langfitt's and Gennarelli's research proposals.

The date for the meeting was set for June 17 and 18 and a tentative agenda was sent to committee members with a request for suggestions as to the manner in which the review should be conducted (Appendix XIII).

A notice of the review was placed in the Penn Paper with a request for members of the University community to send their comments to Dr. Cooperman's office. There were no responses (Appendix VII).

Dr. Richard Rissler, Assistant Director, Animal Health Programs, Veterinary Services of the U.S. Department of Agriculture was advised of the review and invited to be a participant. Dr. Alan L. Sandler, Compliance Officer, Office for Protection from Research Risks at the National Institutes of Health, was also notified and invited to participate. Both Dr. Rissler and Dr. Sandler declined the invitation to be present during the review (Appendix VII).

A room in Logan Hall (the Audiovisual Center) was reserved from June 11 through June 14 to enable committee members to view the video tapes prior to the review. Drs. Asbury, Schiffer, O'Kane and Schnabel spent several hours reviewing tapes during this period.

IV. The Review

On June 17, 1985 the committee convened in the Gates Conference Room on the first floor of the Van Pelt Library at 9:00 a.m. President Hackney opened the meeting and restated the charge (Appendix III). Following President Hackney's remarks the committee in executive session discussed the agenda and the manner in which the review would be conducted. The agenda (Appendix IX) was followed closely with two exceptions which will be commented upon later.

On the morning of the first day, Dr. Langfitt, Dr. Gennarelli and Dr. Thibault spoke of their reasons for undertaking the research, the objectives of the research, the manner in which the research was carried out, and the results of studies in the Laboratory. Later in the morning, the committee heard from two neurosurgical fellows, a research specialist and a neurophysiologist all of whom worked in the Head Injury Laboratory. Following lunch, the committee discussed the studies conducted in the Laboratory and the care of the animals with Dr. Moshe Shalev, Director of the Division of Laboratory and Animal Medicine at the School of Medicine. The committee then paid a visit to the Head Injury Clinical Research Laboratory.

At the time of the committee's constitution, the only tapes available for review were PETA's edited tape "Unnecessary Fuss," a tape of the NIH review, a tape in the camera at the time of the break-in and tapes of subsequent experiments carried out in the Laboratory. The thirty-one tapes stolen by the Animal Liberation Front were delivered to the University of Pennsylvania by the District Attorney's Office and the U.S. Department of Agriculture two weeks prior to the committee's meeting. Although each tape is of two hours length, the time of recorded experiments is far less. Rather than sixty two hours of experiments to review, there were actually twenty-eight hours and fifteen minutes. It was therefore possible for the committee to review all of the tapes. A number of tapes were reviewed twice because of individual reviews the week before.

The whole committee first viewed the video tape entitled "Unnecessary Fuss" edited from the tapes stolen by the Animal Liberation Front. It then viewed a tape of an entire experiment conducted during the review of the Laboratory by the Department of Agriculture and the National Institutes of Health (three committee members, Dr. Schnabel, Dr. Rhoads and Dr. Schiffer, were also present). The committee was then divided into three groups, each group consisting of a member from the faculty of the School of Medicine, a member of the University faculty at large, and a non-University member. Each group received one-third of the remaining tapes which they viewed during the rest of the afternoon.

Earlier in the first day, Dr. Schnabel as chairman of the committee, received a letter from Dr. Gary Francione declining an invitation from the committee to meet with it on the following day (Appendix V). The committee instructed the chairman to contact Dr. Francione and ask him to reconsider his decision not to attend. The chairman finally reached Dr. Francione early on the morning of June 18 and told him of the committee's desire to hear his concerns regarding the studies carried out in the Head Injury Clinical Research Laboratory. Dr. Francione refused to reconsider his position unless he was made a member of the committee. The chairman felt he was not empowered to take such action.

On June 18, 1985 the committee met consecutively with Provost Thomas Ehrlich, two Chairmen of the Animal Care Committee of the School of Medicine, Drs. Aron Fisher and Alan Rosenquist, and Drs. Langfitt, Gennarelli and Thibault. The morning session was completed by an interview with Dr. Alan Klide, Section of Anesthesiology of the School of Veterinary Medicine. The entire afternoon was spent discussing the committee's findings and recommendations concerning future studies in the Laboratory.

V. History

In 1970, the Head Injury Center was established at the Philadelphia General Hospital to make possible intensive studies of patients with severe head injuries and at the same time provide them with special care. It was believed that the monitoring of various physiologic functions (intracranial pressure, cerebral metabolic rate and cerebral blood flow) would lead to better patient care and also provide new insights into the relationship between brain swelling and increased intracranial pressure and mortality and morbidity from head injuries in human beings. The Center was supported by funds from the Philadelphia General Hospital and a grant from the National Institutes of Health. It was directed by Dr. Thomas Langfitt, Professor of Neurosurgery and Chairman of the Division of Neurosurgery at the University of Pennsylvania School of Medicine.

During the first year and a half, the grant from the National Institutes of Health solely supported studies of patients in the Clinical Research Center at the Philadelphia General Hospital. Subsequently, the grant continued to support clinical studies in head-injured humans, and in addition, was extended to studies of head injuries in animals carried out initially in the Hospital of the University of Pennsylvania and at present in the Basic Sciences Building of the University of Pennsylvania School of Medicine. In 1973, the Head Injury Clinical Research Center was transferred to the Hospital of the University of Pennsylvania and the administration of its NIH supporting grant was assumed by the University of Pennsylvania.

In 1970, Dr. Gennarelli and Dr. Ommaya conducted research at the National Institutes of Health on experimental cerebral injuries in monkeys resulting from rapid acceleration and deceleration of the animals' heads. In 1974, experiments using the model developed by Dr. Gennarelli at the NIH were begun in the Head Injury Clinical Research Laboratory in the basement of the Hospital of the University of Pennsylvania. In 1976, Dr. Gennarelli became a member of the faculty of the University of Pennsylvania and continued his studies of head injuries in the Head Injury Clinical Research Center of the University of Pennsylvania. In 1980, the Laboratory was transferred to the basement of the Basic Sciences Building in the Medical School.

Since it was first established in 1970, work carried out in the Head Injury Clinical Research Laboratory has been well known to the NIH by virtue of its submitted proposals, its yearly progress reports, and the

evaluations of the NIH Site Visit Committees. To date, all NIH scientific reviews have been laudatory of the Laboratory's work and have led to its continuous funding.

The animals used in the Laboratory were at first housed with primates used in studies of fertility conducted by the Department of Obstetrics and Gynecology and were under the care of Dr. Flickinger, a qualified Veterinarian.

In 1980, following consultative reports concerning the nature of animal care in the Medical School, Dr. Moshe Shalev was appointed as the first full-time Director of the Division of Laboratory Animal Medicine.

In 1982, Dr. Aron Fisher assumed the chairmanship of the Animal Care Committee. Later that year the committee reviewed a research proposal and an NIH summary statement of the Head Injury Clinical Research Laboratory. The committee also received a report from Dr. Shalev concerning a study that he had witnessed. Dr. Shalev was concerned about experiments which go awry so that animals do not lose consciousness at once. He was also concerned about the long term care of injured animals. The committee withheld approval of the Laboratory's work until it gained further information (Appendix X) concerning compliance of the Laboratory with points seven and nine on page sixty-nine of the Guide for the Use of Experimental Animals.

The Dean of the Medical School, on the advice of the committee, suspended the Laboratory's research activities (Appendix X). Subsequently the committee witnessed a tape of a procedure, interviewed investigators involved in the studies and unanimously approved the continuation of the head injury studies. On March 29, 1983, on the advice of the Animal Care Committee, the Dean of the Medical School released the Laboratory from the research restrictions which he had imposed upon it (Appendix X).

Later reports of the Animal Care Committee indicate that the Laboratory was not in compliance with the Guide's requirement that a qualified veterinarian supervise the animal quarters as well as their care during the studies.

In June 1983, Dr. Shalev became responsible for ordering the animals and supervising their care.

Compliance with the Guide was achieved at a later date when Dr. Shalev and the committee jointly monitored studies in the Laboratory on a regular basis.

The committee was very favorably impressed with Dr. Shalev, both for his caring attitude towards animals and his development of the Division of Laboratory Animals of the University of Pennsylvania School of Medicine.

In May of 1984, over the Memorial Day weekend, the Laboratory was illegally entered and vandalized. Sixty hours of video tape containing records of the experiments were stolen by a group identifying itself as the Animal Liberation Front. Subsequently, copies of the stolen tapes were made available to PETA (People for the Ethical Treatment of Animals) a group resolutely opposed to the use of animals for experiments. PETA then prepared a twenty-four minute tape entitled "Unnecessary Fuss" allegedly selected from the stolen sixty hours of tapes which, it claims, raises serious questions about the moral, legal and scientific aspects of the use of animals in the experiments performed in the Laboratory. PETA has since distributed "Unnecessary Fuss" both nationally and internationally. Many of those who have seen it, have called upon the University to halt the baboon experiments.

In the fall of 1984, some members of the Law School viewed "Unnecessary Fuss" and requested a dialogue on the research, which, with the inclusion of several faculty from the University at large and two faculty members directly involved in the Laboratory's research, was held on January 15, 1985 (Appendix VI).

On January 25, 1985 the faculty of Medicine at the University of Glasgow which has been cooperating in the studies carried out in the Head Injury Clinical Research Laboratory, issued the following statement "that the experiments are conducted under appropriate anesthesia and that the animals are humanely cared for before, during and after the experiments and that care is taken to minimize the number of animals used" (Appendix XI).

More recently, a review carried out by members of the Society for Neuroscience Ad Hoc Investigating Delegation concluded that the work has been in accordance with accepted standards of humane care.

In response to the allegations made against the Head Injury Clinical Research Laboratory, the University stated its wish to conduct another and more comprehensive review of the evidence surrounding the accusations of impropriety in the Laboratory's activities. PETA asked that such a review be conducted largely on the basis of the edited tape "Unnecessary Fuss". The University refused because it felt that the edited tape may have been prepared in a prejudicial manner. Subsequently, with the expectation that all of the tapes would be available for review, the present committee was formed.

On July 18, 1985, one month after the committee's review, the University of Pennsylvania received a report from the NIH of an evaluation of experimental procedures in the Head Injury Clinical Research Laboratory.

VI. General Findings

During the course of its review, it became evident that many shades of opinion existed within the committee on general questions of animal welfare and the suitability of using animals for research purposes. The committee consciously did not address these general questions, but limited itself to the committee's charge which is more narrowly stated. In answering the charge, a clear consensus on the part of all members was reached.

The committee also came to realize that the norms established by the National Institutes of Health in the Guide for the Care and Use of Laboratory Animals as revised in 1978, are not in all instances specific standards but rather, principles which permit some latitude in their interpretation.

Further, it became clear that current techniques used in the Head Injury Clinical Research Laboratory reflect a specific attempt at improving the standards of animal care and use. Undoubtedly, these developments have been stimulated by a rising awareness on the part of both the public and researchers of the sentient nature of laboratory animals.

a. Compliance with NIH Guidelines

The committee appreciates a clear distinction in the degree of compliance by the Head Injury Clinical Research Laboratory with the National Institutes of Health principles for the care and use of experimental animals between past and present methodologies and studies.

During the review the committee noted the following were in non compliance with the Guide: Smoking in the operative suite, lack of aseptic surgical techniques, casual dress, a sub-standard recovery room, incomplete post-operative records and inadequate supervision of the animals by a qualified veterinarian.

The committee believes that these infractions save those involving the care of chronically ill animals have been corrected thereby bringing the Laboratory's acute studies into compliance with the Guide. The Laboratory has already taken note of the inadequacies of the facilities for the long term care of chronic animals and discontinued these studies as of April 4, 1984. No further studies of chronically injured animals will be undertaken until the deficiencies noted have been corrected and the facilities meet the specifications set forth by the Department of Agriculture.

It was also noted that other non-human primate species (i.e., macaques) were being housed in the same animal room as the baboons, contrary to the recommendations of the Guide.

One member of the committee believed that compliance with point nine on page sixty-nine of the Guide, dealing with post-experimental care of animals would be fulfilled if animals that appeared lethargic during the first twenty-four hours following an injury were given a stronger analgesic than tylenol which is used at present.

The committee further agreed that the film "Unnecessary Fuss" gave a distorted view of the conduct of the personnel and the treatment of animals during studies in the Laboratory. While the committee does not condone instances of apparent inappropriate jocularity and offensive comments, it believes they do not reflect the general level of care given the animals or the manner in which the experiments were carried out.

In arriving at these conclusions, the committee gave special attention to the following:

1. Scientific Merit as Judged by:

- a. The Magnitude and Importance of the Problem of Head Injuries
- b. The Experimental Design
- c. Results
- d. Adjuncts to the Baboon Model
- e. Peer Judgement.
2. The State of the Animals, Their Awareness of Pain and Their Care in Both Acute and Chronic Studies:
 - a. Prior to the Injury
 - b. At the Time of Injury
 - c. During the Post-Injury Period
 - d. At the Time of Sacrifice.
3. The Placement and Removal of the Helmet.
4. Review and Monitoring of the Studies.
5. The Facilities.
6. The Conduct and Demeanor of the Laboratory Personnel.

VII. Specific Findings

1. Scientific Merit

The committee was unanimous in its belief that the study of head injuries as carried out in the Head Injury Clinical Research Laboratory at the University of Pennsylvania is of great importance to human welfare with the expectation that the information gained from the studies during the past ten years may lead to ways in which a significant reduction in the morbidity and mortality due to head trauma might be achieved.

a. The Magnitude and Importance of Head Injuries

Head injuries are a major health problem affecting two million individuals in the country each year. There are four hundred thousand hospitalizations with fifty thousand deaths, half of which are sustained during vehicular accidents. The cost to the public is estimated at \$25 billion per year.

b. The Experimental Design.

Head injuries are caused in two ways:

1. By a direct blow (hammer effect) which often damages the skull as well as the brain.
2. Sudden acceleration or deceleration of the head causing the brain to move and momentarily deform within the calvarium.

Head injuries sustained by humans especially in vehicular accidents are often complicated by severe injuries to other organs in the body, making clinical study of the effects of trauma to the brain difficult. The experiments carried out in the Head Injury Clinical Research Laboratory were designed to cause brain injury by a sudden change in inertial force without producing injuries to other organs in the animal's body.

Baboons were chosen as experimental animals because of 1) the similarity of their skulls and brains to humans and 2) the ability to produce changes in inertial force which would result in brain injuries comparable to those seen in humans involved in vehicular accidents.

c. The Results

The work in the Head Injury Clinical Research Laboratory has resulted in new and important findings concerning the nature of the physical forces that cause injury to the brain and in addition has led to a better understanding of the biological processes occurring in brain subjected to trauma. Examples of the new information concerning the causes of brain damage, essential to the development of ways in which brain injuries might be prevented, are as follows:

1. The angle of acceleration is the most important factor in producing acceleration damage to the brain.
2. Angular acceleration causes primary traumatic coma including cerebral concussion and most acute sub-dural hematomas, the two injuries that are leading causes of death and disability from head injuries.
3. The length of time that the head is accelerated plays an important role in determining whether brain damage is vascular (to blood vessels) or axonal (to nerve fibers).
4. The direction of head motion is important in determining the location of damage within the brain and in particular, determines the amount of damage to the brain stem.
5. All clinically important types of brain damage can be produced by appropriate amounts of angular acceleration.

6. Animal models of all clinically important types of brain damage can be reproduced at will.
7. Results obtained in animals can be directly related to human accident situations.

Examples of new information concerning the biologic changes that occur following brain trauma which ultimately may lead to improved treatment of brain injured patients are as follows:

1. Immediately after severe brain injury, profound alterations in cardiac and respiratory function occur which adversely affect the outcome, but these events revert to normal and are not detectable several minutes later when patients receive their first medical examination.
2. Diffuse axonal injury, a specific lesion characterized extensively by this research group, is an important cause of traumatic coma.
3. Concussion (minor head injury) is associated with structural damage to the brain.
4. Primary traumatic coma ranges from minor injury with recovery to severe injury with death and this spectrum is caused by the same type of brain damage (diffuse axonal injury) differing only in amount.
5. Most damaged axons are not severed at the time of injury.
6. Partially damaged axons undergo secondary (delayed) degeneration, converting the damage from a potentially reversible to an irreversible state.
7. Viewing primary traumatic coma as due to axonal damage is a fundamentally new conceptualization of brain injuries.

d. Adjuncts to the Baboon Model

The committee was impressed on learning about the Head Injury Group's development of adjunct physical and in vitro models. Their use of gel simulations of brain material, giant squid axons and guinea pig optic nerves have supplemented the baboon study and decreased the actual numbers of non-human primates needed. All of the committee members considered the Head Injury Group exemplary in this regard. The extent to which these adjunct methodologies are used is expected to increase. During the coming year, 85% of the studies planned by the Laboratory will be of this adjunctive type.

e. Peer Judgment

Grants awarded to the Head Injury Clinical Research Laboratory have uniformly received meritorious marks when peer reviewed by Study Sections appointed by the National Institutes of Health.

2. State of the Animals, Their Awareness to Pain and Their Care in the Acute and Chronic Studies

Recognizing that it is impossible to know under all circumstances whether an animal suffers, or does or does not feel pain, the committee agreed that in general, studies carried out in the Head Injury Clinical Research Laboratory were conducted in a manner that met the requirements of the NIH guidelines with regard to the humane treatment of the animals with the avoidance of unnecessary pain and suffering.

The committee was especially concerned with the pre-injury and post-injury care of the animals and enlisted the aid of Dr. Alan Klide, Section of Anesthesiology at the School of Veterinary Medicine, to help in its assessment of the adequacy of anesthesia during the studies. Dr. Klide was most helpful in his discussion of the anesthetic agents that were used and their effects on animal behavior and awareness of pain. Since he had not reviewed the tapes he was not asked to give an opinion as to the level of anesthesia in the animals prior to injury. He did however, state that unanesthetized baboons ordinarily would exhibit a much more violent type of activity than that noted by the committee just before the injury took place.

a. Pre-Injury

Three types of anesthetic agents are used in the studies carried out in the Head Injury Clinical Research Laboratory: 1) A dissociative anesthetic agent, originally phencyclidine, given prior to the transportation of the animal to the Laboratory, currently ketamine supplemented by Innovar-Vet as needed; 2) a local anesthetic agent, 1% xylocaine, injected at the site of insertion of the recording devices in blood vessels; and 3) a general anesthetic, nitrous oxide, inhaled while recording de-

vices are being placed on the skull and adjacent to the brain and while the head is positioned in the helmet and the injury producing apparatus. The general (inhaled) anesthetic is discussed first.

Most members of the public equate the term "anesthetized" with being unconscious — eyes closed, motionless, unresponsive to external stimuli of a verbal or painful nature. General anesthetic agents such as nitrous oxide cause just such an unconscious state through their depressant action on brain function. The effects of nitrous oxide on cerebral function are rapidly dissipated once the gas ceases to be inhaled, and the animal or patient soon thereafter becomes conscious. In the studies in the Head Injury Laboratory, use of nitrous oxide is ideal during the preparation of the animal but if it were continued through the moment of injury, it would make the pre and post-injury neurological evaluation of the animal useless. Therefore nitrous oxide is discontinued up to an hour before the injury is sustained. In those rare instances when the studies went awry, nitrous oxide was reinstituted and the animal rendered unconscious rapidly.

A second group of anesthetic agents is used to produce local or regional lack of pain sensation. Spinal anesthesia, caudal anesthesia and local anesthesia of the skin and muscles producing regional or local absence of pain are examples of this type of anesthesia. In the animal studies in question, those sites at which recording devices are inserted transcutaneously into blood vessels are rendered anesthetic through the use of 1% xylocaine injections into the tissues locally.

A third type of anesthetic agent produces a dissociative form of anesthesia, that is the patient or animal appears conscious with eyes open, lids blinking, corneal reflexes intact, capable of moving all extremities, yet apparently unaware of pain produced by noxious stimuli such as a pinch or the cutting of the skin and muscles during an operation. Humans undergoing neurosurgical procedures often appear awake, are capable of obeying commands yet apparently perceive no pain. In its review of the tapes, the committee noted that following the cessation of nitrous oxide and during the neurological evaluation just prior to the injury, it was stated in some instances that the animal was awake, eyes open, lids blinking and corneal reflexes brisk. At the same time some animals twisted sporadically on the table in an apparent effort to turn over.

In early studies when phencyclidine was used, the committee felt the activity and movements of the animals prior to injury were slow and far different than the extremely active, noisy and hostile state of the unanesthetized baboons they visited in the animal quarters. The committee was also told that records of pulse, respiration and blood pressure were stable despite the animals' movements and that electroencephalograms showed evidence of an anesthetic effect.

The nature of the animals' movements and the stability of the recorded physiologic parameters led the committee to believe that the effects of the dissociative drug were still present despite the animals' movements and statements that they were awake.

In the review conducted by the NIH when the present regime of ketamine with supplements of Innovar-Vet was used and nitrous oxide was continued until minutes before the injury, one committee member in attendance confirmed a complete absence of voluntary movement and a lack of response by the animal to deep stimuli before and after the injury.

It was noted that contrary to reports in published articles, phencyclidine was not administered intraperitoneally.

b. At the Time of Injury

All members of the committee were convinced that the injury itself was painless in that coma supervened within 4 to 5 one thousandths of a second after injury. This is far shorter than the reaction time required to experience the perception of pain. It is to be noted that patients rendered comatose by head injury rarely recall any pain at the time of injury.

c. Post-Injury

Some concern was expressed for the care given the animals in the post-operative phase, especially those that were rendered comatose and allowed to recover after various periods of unconsciousness. One member of the committee, as previously noted, felt that those animals receiving minimal injuries should be given a stronger analgesic than tylenol which is the present routine. The committee felt that post-oper-

ative care in some of the chronically injured animals was not well documented, because records contained only sporadic entries concerning the fluid input and output and other aspects of general care of the animals. As a rule, records of the animals' general status were not comparable to those appearing in a patient's record in the hospital. In contrast, notes documenting neurological status were of good quality. The actual care rendered must have been continuous and of high quality, given the high survival rates of comatose and encephalopathic animals for weeks following severe injury.

d. At the Time of Sacrifice

The committee was in complete agreement that those animals sacrificed after the production of a head injury were adequately anesthetized.

3. Placement and Removal of the Helmet

One of the major efforts of the Laboratory has been to develop a methodology for delivering a non-impact acceleration force to the animal's head. To do so, it is essential that the animal's head be tightly coupled to the head injury device so that movement of the animal's head exactly mimics movement of the head injury apparatus.

Initially a plastic helmet, which was molded so as to conform to the animal's head, was used in the coupling process. Subsequently to improve the coupling of the injury producing apparatus and the animal's head, a metal helmet filled with dental stone, a rapidly solidifying material, has been used.

The committee noted that in earlier studies, this technique sometimes led to the use of a hammer and screwdriver to remove the helmet when the dental stone adhered to the scalp or the inside of the helmet. By changing the mixture of the dental stone, lubricating the inner surface of the helmet with vaseline and covering the animal's head with vaseline and parafilm, problems associated with the removal of the animal's head from the helmet are now far less common.

The committee was convinced that the forces delivered by the hammering were of far less magnitude than those delivered by the head injury apparatus and did not in any way vitiate the findings obtained during the studies. Nor did the committee feel that the animals suffered or were aware of pain because of their comatose state or the continuing effects of the dissociative drug.

4. Review and Monitoring of Studies in the Laboratory

The committee believes that the review and monitoring of studies carried out in the Head Injury Clinical Research Laboratory has evolved in a steadily improving way from the time of the Laboratory's inception until the present and is now in accord with guidelines set forth by the National Institutes of Health to assure the humane treatment of experimental animals.

Further the committee believes that the University should establish an institution-wide mechanism for the review and monitoring of all studies involving animals, comparable to the review and monitoring of human studies which it now conducts. Finally, the committee feels that this review process should be broadly based and include a layperson or persons not members of the University community and a person or persons not involved in research using animals.

5. The Facilities

Initially the Head Injury Clinical Research Laboratory was located in the basement of the Hospital of the University of Pennsylvania. In 1980, due to hospital construction it was moved to the basement of the Basic Sciences Building of the Medical School. The Laboratory, out of necessity, was placed in the basement of the Medical School Building since the forces generated by the head injury device demanded a six foot cube of cement as a base. The Laboratory consists of a main room housing the head injury device and an operating table which is separated by a partial wall from the controls for the machine and various recording devices. At the far end of the room, partially separated from the main room, is the recovery room where animals are cared for who have received more serious injuries. A separate office completes the Laboratory facilities.

During the past two years construction on the floor above has created some problems with cleanliness and dust in the Laboratory. During its visit the committee learned that the Department of Agriculture judged

the recovery area to need numerous renovations before it would meet standards of the animal Welfare Act. The room currently has a dropped ceiling design which is difficult to clean and could harbor vermin and is also used as a workshop for equipment, both of which are not in compliance with the Guide.

6. Conduct and Demeanor of the Laboratory Personnel

Interviews with the current members of the Head Injury Clinical Research Laboratory revealed them to be sensitive individuals who treated and cared for the animals in a humane way. Further they confirmed an openness on Dr. Gennarelli's part to suggestions they made periodically for improving the care and use of the baboons.

Remarks and actions which appear to indicate a lack of respect for the experimental animals are primarily attributable to one individual who worked in the Laboratory over a three month period. In contrast to his demeanor on video tape, the same person also spent a number of nights personally caring for animals with chronic injuries.

While the committee cannot condone an unclean Laboratory, the remarks made by those involved in the studies seem to indicate their concern about a temporarily unsatisfactory situation and the efforts that they were making to have it remedied. At the time of the NIH Committee review the three members of the Committee who were present felt that the degree of cleanliness was satisfactory.

The importance of the lack of aseptic techniques and casual dress of the investigators to the well-being of the animals was hard to evaluate since the majority of experiments were of an acute nature with sacrifice of the animal shortly after the injury. In addition, infections in the chronically injured animals appeared to be very few in number. Nonetheless, the committee believes that regardless of the nature of the study, aseptic techniques should be observed in all studies carried out in the future.

III. Conclusions

The Committee finds that the Head Injury Clinical Research Laboratory has made significant changes and improvements in accordance with the National Institutes of Health guidelines and principles governing the care and use of laboratory animals and that current protocols and facilities, as used for acute studies only, are in compliance with the Guide. The Committee further believes that past infractions noted in this report have ceased to occur as the sensitivity and awareness on the part of the investigators have evolved.

The committee was most impressed by the results of studies in the Laboratory in particular those which have led to an entirely new concept of primary traumatic coma as being due to axonal damage.

Despite the diverse backgrounds of the committee members and their wide range of opinion on the general question of the use of animals in research, the committee strongly believes that in view of the dimensions and importance of the human problem, that the investigators

should be encouraged to carry the work forward in the belief that it will ameliorate the poor results now attainable by standard methods for the treatment of head injuries.

Recommendations

1) *That in accord with the New Public Health Service Policy on Institutional Animal Care and Use Committees, all research involving animals at the University of Pennsylvania be reviewed and monitored in a manner similar to that used to review and monitor human studies and that the review and monitoring of animal research be carried out by the currently existing University of Pennsylvania Institutional Animal Care and Use Committee.*

2) *That no studies of chronically injured animals be undertaken until facilities for post-operative care meet the standards of the Animal Welfare Act and the Guide.*

3) *That the University of Pennsylvania Institutional Animal Care and Use Committee review and approve all chronic studies carried out in the future by the Head Injury Clinical Research Laboratory.*

4) *That the University of Pennsylvania Animal Care and Use Committee approve any change in the current protocols used for acute animal studies.*

5) *That the University of Pennsylvania Institutional Animal Care and Use Committee carefully monitor animal care in the pre-and post-injury period.*

6) *That there be documentation of an insensitivity to pain on the part of the animals prior to injury.*

7) *That all non-human primate studies be conducted using aseptic surgical techniques.*

8) *That the Laboratory continue its efforts to minimize the use of non-human primates by increasing studies of other types of models.*

9) *That the responsible investigators increase their efforts to inform the public of the nature of studies carried out in the Head Injury Clinical Research Laboratory.*

Committee to Review The Head Injury Clinical Research Laboratory of the School of Medicine

Dr. Truman G. Schnabel, Chairman

Dr. Arthur K. Asbury

Dr. Abraham Edel

Rev. Frank M. Harron

Mr. Erik Hendricks

Mrs. Pauline Innis

Dr. Daniel J. O'Kane

Dr. Jonathan E. Rhoads

Dr. Stephen P. Schiffer