Almost one hundred and eighty years ago, delegates from thirteen sovereign states gathered in Philadelphia, Pennsylvania, to formulate a bold and imaginative political concept—government by consent. Today, it is both our burden and honor to apply in very specific instances the general principle enunciated at that time —informed consent—be that of the governed or the patient. The founding fathers were concerned then, as we are concerned now, with balancing the welfare of society against the protection of the individual.

informed consent

by B. Harvey Minchew, M.D., and C. Gallogly

The broad remedial legislation of the Food and Drugs Act of 1906 was a reaction to a clear and present danger to the health of the entire Nation. More specific legislation was enacted, often following in the aftermath of a national tragedy. Full appreciation of the need for pretesting and preclearance of drugs arose out of the death of approximately 100 persons in 1938 after taking sulfanilamide dissolved in diethylene glycol—a compound which is known to be a very effective antifreeze. The result of this tragedy was the enactment of the Food, Drug, and Cosmetic Act of 1938. Under the 1938 law, before a new drug could be introduced into interstate commerce, the manufacturer was required to submit proof of safety for its proposed use or uses.

Thus, from 1938 until 1962, the manufacturers of drugs were required by law to provide the Food and Drug Administration with acceptable evidence that a drug was *safe* for its proposed use. They were not required, with the exception of certified antibiotics, to demonstrate that the drugs were effective. Likewise, prior to 1962, there was virtually no Government regulation over the investigational studies which were required for premarket-

ing clearance of a new drug.

Under those early controls several unsafe practices developed. In some instances the distribution of an investigational drug was so widespread that promotion and marketing rather than investigation appeared to be occurring. There was, furthermore, no way of insuring that adequate manufacturing controls or adequate preclinical tests were done before the investigational drug was first used on humans. Additionally, the informed consent of a person used in investigational studies was in no way guaranteed. In fact, it was stated in congressional hearings on this subject that there were no statutes in any of the States which required that a patient be informed if he were to receive an experimental drug.

It is not often that the American public becomes familiar with the toxic effects of a specific drug and even rarer still when merely the mention of that name is capable of recalling how close we came at one time to another national tragedy—but thalidomide is such a name. Although, in this instance, major tragedy in this country was averted, the regulatory inadequacy was obvious. Here was an investigational drug, distributed and used by the recipient without the knowledge that the drug had not been cleared for safety by the Food and Drug Administration.

The constant concern expressed in the press as well as in both Houses of Congress was—Why had this investigational drug been distributed and used by patients who had not been informed of the risk they might be assuming, and, therefore, could not intelligently consent to such a risk. The practice of using an uninformed human for investigational purposes runs contrary both to national policy and personal belief. Notwithstanding any possible benefit to society in general, our system is based upon the intelligent response of an informed individual.

The 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act emphasized that both *safety and effectiveness* of drugs are primary objectives of the law. In general, the amendments provided for new means of assuring the attainment of these national objectives in the areas of investigational drug research, manufacturing, distribution, advertising, and labeling of drugs.

Unless a drug is generally recognized among qualified experts as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, it is defined by law as a "new drug." Therefore, a new drug which has not received FDA approval for marketing is "investigational" in nature and may be shipped in interstate commerce only when the proposed plan of investigational study is on file with our Agency.

Before any new drug receives approval for marketing, the Food and Drug Administration must have *substantial evidence* that the drug will have the effect claimed for it. This approval will not be forthcoming on the basis of shoddy experimentation or incomplete testing or analysis.

It is not sufficient that there merely exists *some* evidence that the drug does what it purports and is represented to do—there must be *substantial evidence* of this fact. We are dealing with probabilities, and it must be sufficiently clear that it is substantially probable that what is claimed will actually occur. The law has further defined *substantial evidence* to mean "evidence consisting of adequate and well controlled investigations, including clinical investigations," by qualified experts, . . . "on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling . . . thereof."

It is during these clinical investigations of new drugs that the law requires the consent of persons used therein. Thus, the 1962 amendments provided that physicians using investigational drugs on human beings must "obtain the consent of such human beings or their representatives except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings."

The Government does not regulate in a vacuum. In implementing these regulations, FDA drew upon national and international experiences with respect to human experimentation so as to learn from these documents and experiences how best to attain these sought-after goals.

Particular attention was paid to the Nuremberg Code. The experimentation on human beings by Nazi doctors aroused international revulsion, and led to the establishment of a ten-point code to serve as a guide for those carrying out research on human beings. It is of particular importance to note that Point 1, the superstructure upon which this entire code is constituted, states: "the voluntary consent of the human subject is absolutely essential." The nature of this consent and the means by which it is to be obtained are expressed with great specificity. It is stated that the person involved should have the legal capacity to give consent; should be able to exercise free power of choice; and have sufficient knowledge and comprehension of the matter involved so that he can make a value judgment. It is further stated that the duty and responsibility for ascertaining the quality of consent rests upon the individual directing the experiment.

The rapid acceleration in clinical investigation occurring during the decades following the Second World War resulted in the Declaration of Helsinki, which is a series of guidelines adopted by the World Medical Association in 1964 to assist doctors involved in clinical re-

search situations. The necessity for applying the results of laboratory experiments to human beings was recognized, but it was also appreciated that there had to be developed a standard against which each individual doctor could judge the quality and nature of his particular activities.

The Declaration specifically states that clinical research should be: (1) based on laboratory and animal experiments or other scientifically established facts; (2) conducted only by scientifically qualified persons under the supervision of a qualified medical man; (3) preceded by careful assessment of inherent risks in comparison to foreseeable benefit to the subjects or others; and (4) that the human being, be he patient or the object of clinical research, should be fully informed and must freely consent. The Declaration makes the fundamental distinction between clinical research in which the aim is essentially therapeutic for a patient, and clinical research the essential object of which is purely scientific and without therapeutic value to the person subjected to the research. In 1966, the Declaration was endorsed by major medical organizations in the United States.

Reflecting the growing Government concern with this problem, the Public Health Service made effective in July of 1966 a policy which extended the requirement of prior review of all research involving human beings to all grants and awards in the support of research, training, or demonstration projects. The subject of this memorandum was "Investigations Involving Human Subjects, including Clinical Research: Requirements for Review to Insure the Rights and Welfare of Individuals." Thus, the Public Health Service requires that it is the responsibility of the institution to which the grant is awarded to provide "prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should 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. A description of the committee of the associates who will provide the review shall be included in the application."

The American Medical Association in endorsing the ethical principles set forth in the Declaration of Helsinki accepted them as accurately expressing the fundamental concepts already embodied in the *Principles of Medical Ethics* of the AMA. The "Ethical Guidelines for Clinical Investigation" adopted by the House of Delegates of the AMA in November 1966 enlarged upon those fundamental concepts. These guidelines were intended to aid physicians in fulfilling their ethical responsibility while engaged in the clinical investigation of new drugs and procedures. Generally speaking, a doctor may participate in clinical investigations only as part of a systematic program employing accepted standards of scientific research calculated to produce valid and significant scientific data. The investigator must demonstrate the same concern and caution for the welfare, safety, and comfort of the person involved as is required of a physician attending a patient independent of any clinical investigation.

Further spelling out the details of the "Ethical Guidelines for Clinical Investigation," the AMA has emphasized the following: In a clinical investigation primarily for treatment, the physician is naturally expected to exercise his professional judgment and skill in the best interest of his patient. Further, voluntary consent must be obtained from the patient or his legal representative if necessary. This consent should be attained only after the physician discloses that he intends to use an investigational drug or experimental procedure, and explains the nature of the drug or procedure to be used as well as the risks involved and the possible therapeutic benefits. An offer to answer any inquiries should be made and the disclosure of alternative drugs or procedures should be explained. Ordinarily, this consent should be in writing. An exception is made where the physician deems it necessary because of the particular circumstances to rely upon consent in other than a written form. The *assumption* of consent is permissible only where the patient in an emergency situation is incapable of giving consent and there is no one available who has the authority to act on his behalf. It is also deemed appropriate in exceptional circumstances to withhold requesting consent from the patient where such disclosure would be detrimental to the best interests of the patient. In such circumstances this information must be disclosed to a responsible relative or friend of the patient when possible.

In a clinical investigation primarily for the accumulation of scientific knowledge, adequate safeguards must be provided for the welfare, safety, and comfort of the subject. In this instance, consent must be in writing from the subject or his legally authorized representative and again only after disclosure that an investigational drug or procedure is being used, an explanation of the procedure and risks involved, as well as an offer to answer any inquiries on the drug or procedure. No person may be used as a subject against his will. Minors or mentally incompetent people may be used as subjects when the nature of the investigation requires their particular participation and consent in writing is given by a legally authorized representative acting in circumstances in which an informed and prudent adult would reasonably be expected to volunteer himself or his child as a subject.

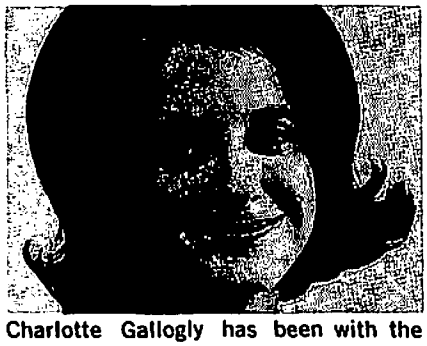
In August 1966, and in March 1967, the Food and Drug Adminis-

tration codified what was already the accepted practice in the medical profession in the form of proposed regulations.

The August 1966 regulations were issued to meet the apparent need for specific guidelines on how consent is to be obtained and what exceptions are to be allowed. An understanding of these guideline regulations requires appreciation of the terminology commonly used in the clinical investigation of new drugs. Such investigations are divided into three phases. *Phase 1* studies are those when a drug is first tried in human beings. Prior to these studies only animal and *in vitro* data are available. The purpose of this phase is to determine basic human toxicity, metabolism, absorption, elimination, other pharmacological action, preferred route of administration, and safe dosage range. *Phase 2* covers the initial trials on a limited number of patients for specific disease control or prophylactic purposes. *Phase 3* is the actual clinical trial designed to assess the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. Under the August 1966 regulations, clinical investigators studying investigational new drugs are required to obtain the written consent of patients for the use of investigational drugs, except in unusual circumstances. Exceptional or unusual cases would occur when it would not be feasible to obtain patient consent or the consent of his representative, or where it would be contrary to the patient's welfare to obtain his consent. Examples of such cases would be when a patient is in a coma or is otherwise incapable of giving informed consent, his representative cannot be reached, and when it is imperative to administer the drug without delay; or 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 interest would suffer if consent were sought—such as in some patients with malignant diseases.

In order to give informed consent, the patient must have the legal capacity to give consent, be able to exercise free power of choice, and be provided with a fair explanation of all material information concerning the administration of the investigational drug—or his possible use as a control—so as to enable him to make an understanding decision as to his willingness to receive the drug. This latter element requires that the investigator should make known to the patient the nature, duration, and purpose of the drug's use; the method and means by which it is to be administered; all inconveniences and hazards that could reasonably be expected; the existence of alternative forms of therapy; and the effects upon his health or personality that may come from administration of the investigational drug.

After consideration of the comments made by the American Medical Association, other professional groups, the Pharmaceutical Manufacturers Association, the National Academy of Sciences, and other Government agencies, the Food and Drug Administration, in March of 1967, issued proposed regulations which modified the guidelines defining procedures for carrying out the patient-consent requirements.



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In these proposed revisions the consent of a person receiving an investigational drug is still required in writing in *Phases 1* and *2* of clinical investigations. Written consent is deemed necessary during these phases since the toxic potential of the drug is relatively unknown, and because the basic purpose of these phases is the accumulation of scientific information, and possible therapeutic benefit to the patient is not yet defined. It is in *Phase 3,* in which a number of investigators are using the drug on patients essentially as it would be used if approved for medical use, that FDA modified the guidelines. In this last phase it is the responsibility of the investigators, taking into consideration the physical and mental state of the patient, to decide when it is necessary or preferable to obtain consent in other than the written form. When such written consent is not obtained, the investigator must obtain oral consent and record that fact in the medical record of the person receiving the drug. The investigator, however, is required in all phases of clinical trials to give the patient "pertinent information" on the investigational drug.

After consideration of the comments received, FDA published an order on June 20, 1967, making the patient-consent regulations final without change. In complying with the regulations, the medical profession is not faced with the ultimate choice of protection to the individual at the cost of eliminating experimentation, but merely with an added procedural device by which we can be assured that the overriding public policy—the right to informed consent—is guaranteed.