

## Physiologic and Pharmacologic Studies in Human Volunteers

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THIS ESSAY concerns some of the ethical, practical, and legal problems associated with studies in man, both awake and in the anesthetized state. We discuss the use of human volunteers through consideration of the following issues: 1) the rights and welfare of the volunteer; 2) informed consent; 3) preparation for the study and implementation of the plan; 4) obligation to terminate the study before completion under certain circumstances; 5) the risk-benefit relationship; 6) liability for injury to the volunteer.

### The Rights and Welfare of the Volunteer

Concepts of the physician's ethical behavior and his concern for the patient's welfare are at least as old as the Hippocratic oath. There it is stated, "I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous." This code is still applicable to the traditional doctor-patient relationship, which has been characterized as a therapeutic alliance.<sup>1</sup> Clinical research has been able to proceed under this umbrella because the physician is, in fact, seeking therapeutic results. The patient may benefit from the research. But, with the burgeoning of experimental medicine, a new relationship has emerged—that of the physician experimenter and his subject, not a therapeutic but a scientific alliance. To this new partnership the physician rightly brings his traditional ethical codes. But these codes must be enlarged and interpreted to include the many new possi-

bilities presented by a scientific partnership, where the patient-subject is unlikely to benefit medically from the risk he accepts. Perhaps others will benefit now, or in future generations. Thus, today's physician-experimenter finds himself acting in the best interests, not of his own subject-patient, but of a collective group of other patients. The physician may thus become responsible as much to society as to his patient. In such a setting it can become all too easy to excuse minor risks, or slight injuries, as a small sacrifice for the general welfare. Greater excesses might then follow. Such an excuse has been offered as partial justification for the medical experimentation which occurred in Hitler's Germany. It was in reaction to such atrocities that the Military Tribunal in 1947 promulgated the Nuremberg Code (Appendix I). There are ten points in this document on the proper conduct of medical research, with points 4 and 5 most specifically concerned with the welfare and integrity of the human subject.

The document of the Military Tribunal was followed in 1964 by the World Medical Association's Declaration of Helsinki (Appendix II). The sense of this document is similar to that of the Nuremberg Code, but there are differences in details. One is the separation of therapeutic from nontherapeutic clinical research, with the promulgation of slightly different guidelines for the two. For instance, the necessity to obtain informed consent in therapeutic research is tempered by considerations of patient psychology.

From the Nuremberg and Helsinki documents have been derived the National Institutes of Health Regulations and the American Medical Association's *Ethical Guidelines for Clinical Investigation*. We do not lack codes for ethical behavior in human experimentation. Let us hope our common sense and conscien-

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tious concern allow us to apply the guidelines wisely.

### Informed Consent

The first and longest section in the Nuremberg Code is concerned with informed consent. This probably reflects the court's reaction to the involuntary participation of prisoners during the war years. Strict interpretation of the Nuremberg requirements would interfere with certain kinds of clinical research, where totally informed consent might prejudice the results (*e.g.*, double-blind studies). It would also preclude the experimental study of minors, comatose patients, and the mentally retarded. In recognition of such problems the Helsinki code broadened the concept of informed consent, suggesting means of handling these situations.

It is regarding informed consent that many have taken the most pessimistic views. How, they ask, can consent be truly informed, unless the volunteer attends medical school for four years?<sup>2</sup> The "competence gap" between subject and experimenter<sup>3</sup> must widen into an abyss as we move from medical volunteer, through educated professional and student, to the less well educated, prisoners, children, and the mentally retarded. As a result some have despaired of the possibility of obtaining informed consent from the average individual. They have rejected participation of the poor for financial reward as a "volunteer" activity, identifying a coercive aspect when the experimenter promises money to one who has empty pockets. They point to "volunteering" in prison as avoidance behavior related to shabby conditions, and evidence for this viewpoint exists.<sup>4</sup> Their suggestion is, therefore, participation by the experimenter as subject; and when more subjects are needed, let the experimenter interest those who are best informed, least in need of money, and most highly motivated to participate for humanitarian reasons.<sup>5</sup> That such a philosophy will sharply reduce the available pool of volunteers and may even produce a nonrepresentative cross-section of subjects is realized. That it will more clearly recognize the rights and dignity of individuals is offered as philosophical compensation for the inevitable scientific slowdown.

Differing from the school which places such human concerns strictly beyond negotiation are the pragmatists who advocate consent modulated by societal controls yet to be developed, placed in the hands of eleemosynary institutions, with governmental intervention taking place only in case of abuses or excesses.<sup>6</sup>

The present methods of the concerned practicing research scientist may be illustrated by describing our own means of achieving informed consent. Potential volunteers are interviewed for 45 minutes by a senior experimenter, who describes the study and its purposes in detail. The consent form is reviewed and each procedure is described in medical and in lay language. The interviewee is taken to see a study in progress if one is under way, and if not, he is shown color pictures of a human study. The likely hazards are described, and a statement affirming our legal responsibilities and our moral obligation to right any injuries and compensate the subject fully for them is made. The volunteer's questions are answered, but he is not permitted to agree to participate at the initial interview. As evidence of thoughtful consideration and voluntary participation he is required to make another appointment to see the interviewer—a day to a week later. At the second interview the study protocol and consent form are again reviewed, and the potential volunteer may then agree to participate and sign the consent form. A sample form is shown in figure 1.

The form is not overly long, and much detailed information which could be included is omitted. We offer as our rationale these three arguments: 1) Epstein and Lasagna have demonstrated that comprehension of the consent form by potential subjects is inversely related to its length.<sup>7</sup> 2) A full oral explanation is given when the volunteer is interviewed and questions are answered at that time. 3) The subject's consent is based, at least in part, upon trust in the experimental group; the experimenters are morally obligated to expend all efforts on behalf of the volunteer regardless of what documents are signed.

Several likely hazards are specified in the consent form, as is the fact that unforeseen difficulties could arise. Even though certain risks are known to be present and potentially

greater undefined risks lurk in the background, volunteers nevertheless agree to participate. We believe they consent because they trust the experimenters, and because the experimenters have themselves been subjects in similar studies. In this connection, Point 5 of the Nuremberg Code suggests that, when a risk must be incurred, it might be acceptable in consenting volunteers if the experimental physicians themselves volunteer to be subjects as well. However, this idea has not worn well in some quarters. We, who have participated as subjects in human studies, have been told by some that while *we* may be foolhardy, this provides little reason for risking the health and welfare of others. We do not presume to judge whether the experimenter himself should be a subject, but only set forth the issues involved in human experimentation and describe some of our own practices.

#### Preparation for the Study and Implementation of the Plan

How are we to insure adequate preparation and skillful implementation? At present the best mechanisms seem to be peer review of the experimental protocol. This concept appears to have been first formulated early in the nineteenth century by Thomas Percival, in his *Medical Ethics*:

Whenever cases occur, attended with circumstances not heretofore observed, or in which the ordinary modes of practice have been attempted without success, it is for the public good, and in an especial degree advantageous to the poor (who, being the most numerous class of society, are the greatest beneficiaries of the healing art) that new remedies and new methods of surgical treatment should be devised. But in the accomplishment of this salutary purpose, the gentlemen of the faculty should be scrupulously and conscientiously governed by sound reason, just analogy, or well authenticated facts. And no such trials should be instituted without a previous consultation of the physicians or surgeons according to the nature of the case.

The utilization of peer review has grown. Government regulations now require this mechanism at all institutions where federal funds are used for human research. For details on the workings of this mechanism at one institution, see the report of Melmon and colleagues.<sup>9</sup>

Specifically, preparations for human experimentation should include evaluation of previous animal studies and knowledge in depth of the problem to be investigated. It is expected that, starting from such a base, a good experimental design can be formulated (Point 3 of the Nuremberg Code).

Adequate preparations must be made and facilities provided to prevent, and if necessary, to treat even remote possibilities of injury to the subject (Point 7). Point 8 of the Nuremberg Code demands the highest degree of skill and care in conduct of the experiment by scientifically qualified persons. How compliance with these requirements is attempted in our laboratories will be described in part.

After informed consent has been obtained, a medical history is taken, a physical examination performed, and screening laboratory tests are ordered, including blood count, chemistries, electrocardiogram and chest x-ray. An abnormality in any of the above precludes participation in the experiment.

The precautions taken during the period of study include elaborate monitoring and preparations for some rather unlikely events, including cardiac arrest (a dc defibrillator is in the room whenever a volunteer is anesthetized). To be sure, such precautions may not be taken during many anesthetics, but the experimenter-subject relationship is a special one. The volunteer enters the hospital in good health and the experimenter must bend over backwards to insure that he leaves in good health.

Following the study, overnight hospitalization is almost always advisable, even if anesthetics have not been administered. It prevents the volunteer from doing harm to himself by excesses of behavior in the immediate post-study period, and it permits re-examination by the experimenter the following morning when the hospital discharge note is written. A follow-up visit is scheduled about a week later, when possible delayed difficulties may be detected. In order to insure that this follow-up visit takes place, about 20 per cent of the volunteer's fee is withheld until he returns. Any complications call for additional visits and treatment. If there are no difficulties, a final note is written, and the patient is discharged from our care. Evidence of individual satisfaction may be gleaned from the fact that some return for later studies, and

PHYSIOLOGIC STUDIES DURING CYCLOPROPANE ANESTHESIA

I, \_\_\_\_\_, am over 21 years of age and am in good health. I volunteer to serve as a subject for physiologic studies during general anesthesia. While I am being paid for my participation in this investigation, I am participating also out of an interest in learning how medical research is conducted and through a desire to further the advancement of knowledge.

I will be anesthetized with oxygen and cyclopropane, a commonly used but potentially explosive gas. Once asleep, my muscles will be paralyzed with a drug (*d*-tubocurarine) and its action will be reversed by other drugs at the end of the study (atropine and prostigmine). A breathing tube will be placed through my mouth into my trachea (windpipe), and a machine will control my breathing when I am asleep.

A needle will be inserted through the skin just beneath my ear into the bulb of the jugular vein (main vein from the brain). A catheter (plastic tube) will be placed in an artery in my arm. I understand that blood samples will be taken for a study of the pathways of brain metabolism and for evaluation of my lung function. Part of the time I am breathing this anesthetic it will contain some weakly radioactive inert gas (Krypton<sup>85</sup>) used to measure brain blood flow. Small amounts of sterile salt solution containing a radioactive inert gas (Xenon<sup>133</sup>) will be injected through a fine needle into the muscles of my legs for muscle blood flow measurements. Both radioactive gases will be rapidly eliminated from my body by way of the lungs, and the radiation dose to my whole body will be extremely low. I also understand a weak electrical stimulus will be applied to my wrist for brief periods while I am anesthetized, and the electrical potentials evoked in my brain will be recorded through disc electrodes on my scalp.

I understand that the blood vessels which have been punctured may become sore and the skin at these sites may be black and blue for several days. Nausea and vomiting may also occur as a consequence of the administration of this anesthetic. I have seen a photograph taken during the conduct of such a study. Although the nature and demands of the study are outlined above, I understand that if some unforeseen complication occurs, it too is considered to be one of the hazards of being a volunteer.

Following the study I agree to being admitted to the Hospital of the University of Pennsylvania for observation during the postanesthetic period.

DATE OF INTERVIEW: \_\_\_\_\_ SIGNATURE OF VOLUNTEER: \_\_\_\_\_

DATE OF STUDY: \_\_\_\_\_ SIGNATURE OF PHYSICIAN: \_\_\_\_\_

WITNESS: \_\_\_\_\_

FIG. 1. Sample consent form.

many refer their friends and roommates as potential volunteers. Still others retain their attachment to us, regarding the experimenter somewhat as a family physician. And the most highly motivated and curious return to visit the laboratory, see the experimental results, and ask that copies of the paper emanating from the study be sent to them.

**Obligation to Terminate the Study  
before Completion under  
Certain Circumstances**

The Nuremberg Code provides for termination of an experiment under two circumstances: 1) the reaching of physical or mental limits intolerable to the subject; and 2) the occur-

rence of a circumstance which, in the judgment of the scientist, might be harmful or dangerous to the subject. The Helsinki Declaration recognizes the same two situations, and adds that the subject's guardian should also be free to withdraw permission for continuation of the research. There is here the germ of an idea which we believe should be nurtured. Someone other than the experimenter should be present to act in the sole interest of the subject. The subject may be sedated, or under stress, or even anesthetized. The experimenter's loyalty may be divided between his subject's welfare and the collection of data. An "*amicus voluntarii*" who is not one of the experimenters is more likely to limit his con-

cern to the welfare of the subject. He is better able to stand in the traditional physician-patient relationship and demand termination if, in his opinion, continuation entails unnecessary risk. If the study is being performed with the subject under anesthesia, the anesthetist is the logical *amicus voluntarii*. If no anesthetic is being administered, we have nevertheless appointed a senior staff member to stand "in loco anesthetis" and act as the subject's advocate. In our judgment the presence of such an individual has been worthwhile and should be encouraged in human experimentation.

### The Risk-Benefit Relationship

Points 2 and 6 of the Nuremberg Code require that the benefits which may accrue to society as a result of the experimental study of man exceed the risks. Both the Nuremberg Code and the Helsinki Declaration imply that potentially greater benefits might justify more significant hazards. This essay is unlikely to cast additional light on the centuries-old dichotomy between the rights of the individual and the requirements of society. We propose instead to seek a semiquantitative statement on acceptable degrees of risk, that is, the amount of risk society seems to have condoned, or at least accepted, in other endeavors. Perhaps from these data one can propose goals of safety, or limitation of risk, for human experimentation.

For quantitative consideration of risk, Starr has offered the concept of fatalities per person-hour of exposure.<sup>10</sup> The idea can be illustrated by considering an average man who might live for 75 years, or 660,000 hours. If his risk of dying from natural causes or diseases is spread evenly over his lifetime, the risk is then 1/660,000 per hour of exposure to life. This is more easily expressed as a probability of fatality per person-hour of exposure or  $P_f$ , which can be calculated to be  $1.5 \times 10^{-6}$ . There is an additional risk related to involuntary exposures, e.g., natural disasters such as earthquakes and floods. The  $P_f$  for this risk is far smaller, being in the range of  $10^{-10}$ . Other additional risks which might be characterized as semivoluntary include the use of automobiles and commercial aviation. In these cases the  $P_f$  is close to that for disease,

10<sup>-6</sup>. The highest-risk categories are those entered upon voluntarily, with one of the most dangerous activities being participation in private aviation. For this activity the  $P_f$  is  $3 \times 10^{-5}$ . Thus, there is one fatality per 30,000 hours of exposure per person.

Society has accepted the risk of private aviation for the benefits gained—efficiency of travel, sport, or other motivations. Might we accept an equivalent risk in human experimentation? The relative benefits of these two activities to society would be hard to quantitate, but we might regard a  $P_f$  of  $3 \times 10^{-5}$  as the maximal acceptable risk. The minimal risk we might set as a goal is that accepted in travel by commercial air carrier or motor vehicle, a  $P_f$  of  $10^{-6}$ , or one fatality per million person-hours of exposure. For comparative purposes, one may consider the far greater risk of common diagnostic measures. In patients, catheterization of the left side of the heart, or liver biopsy, are each associated with a  $P_f$  of approximately  $2 \times 10^{-5}$ .<sup>11</sup>

Admittedly, this discussion has considered only fatalities, ignoring the far more common category of injuries. However, there has not yet been an equivalent attempt at quantitation of the risk of injury, or expression of the ratio of injuries to fatalities in various areas of endeavor. In the absence of such analyses we have been forced into the somewhat crude and cold-blooded fatality analysis presented here.

### Liability for Injury to the Volunteer

Liability is not mentioned in the Nuremberg Code or the Helsinki Declaration since these represent primarily moral and ethical, rather than legal, guidelines. Precedents already exist in the law for compensation of injured parties when the injury can be shown due to negligence or dereliction. In the areas of medical care and therapeutic research the legal rules are reasonably well defined.<sup>12</sup> However, in the domain of nontherapeutic research there is a dearth of regulatory statutes and pertinent cases.<sup>12</sup> Still, we might imagine that court decisions would not be difficult where the experimenter could be shown to have been negligent or derelict. New solutions are urgently needed for the compensation of injured parties when no one is obviously

at fault. What remedy has the volunteer who is unintentionally injured in a carefully-designed and well-carried-out study where no one can be shown to have erred? Where is the equivalent of workmen's compensation for human volunteers? In 1960 the concept of "liability without fault" was introduced.<sup>12,14</sup> It would provide protection for the subject in that if injury or damage of any kind occurred he would be entitled to be made whole through treatment or to receive compensation for damages. Should an unfortunate result occur despite the exercise of due care, the experimenter's competence would not be called into question, as it inevitably is with the filing of a malpractice suit.

The idea of no-fault liability is a promising one. It has been espoused by others.<sup>15-17</sup> It remains for those who advocate it to agree on the agency which should pay for and administer it—government, research institutions, insurance companies, or agencies sponsoring the research. And then it remains for an energetic few to bring into being such a system of volunteers' compensation.

### The Future of Human Studies

The study of drugs in man must continue. Clinical research in man is *required* by the Drug Amendments Act of 1962, before a new drug can be licensed.<sup>18</sup> The case for studies in man has been made by many.<sup>19</sup> Moral questions concerned with how these studies are to be carried out remain, and general agreement on some of them may be impossible. Perhaps this is inevitable in an area where science and philosophy are interfaced. This essay has been a status report of our beliefs and practices in human experimentation. Six areas of concern have been identified, and progress in each has been commented upon. While better definition and agreement on some of the large issues would be desirable, it may come only slowly and with difficulty. Three areas in which significant accomplishments may be hoped for in the near future appear to be: 1) more widespread application of the concept of the *amicus voluntarii*; 2) better quantitation of risk-benefit relationships; 3) development of a no-fault compensation system which adequately protects the subjects and the experimenter.

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## APPENDIX I

*The Nuremberg Code*

United States versus Karl Brandt, et al.\*

Nuremberg Military Tribunal

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and

adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

## APPENDIX II

*Declaration of Helsinki**Recommendations Guiding Doctors in Clinical Research*

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964

*Introduction*

It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of The World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration," and the International Code of Medical Ethics which declares that "Any act, or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and the clinical research, the essential object of which is purely scientific and without therapeutic value to the person subjected to the research.

\* United States Adjutant General's Department. 1947. Trials of War Criminals Before Nuremberg Military Tribunals Under Control Council Law No. 10 (October, 1946-April, 1949). The Medical Case, U. S. Government Printing Office, Washington, D. C. Vol. 2: 181-183.

### I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

### II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, re-establishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.

2. The doctor can combine clinical research with professional care, the objective being the

acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

### III. Non-Therapeutic Clinical Research

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.

2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.

3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.

3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.

4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.

4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued.

The investigator or the investigating team should discontinue the research if in his or their judgment, it may, if continued, be harmful to the individual.

## Drugs

**NEUROMUSCULAR BLOCK AND UTERINE ACTIVITY** The effects of competitive and noncompetitive neuromuscular blocking agents on spontaneous and oxytocin-induced activity of human, gravid myometrium strips were studied *in vitro*. The drugs used included succinylcholine, *d*-tubocurarine, gallamine triethiodide, and decamethonium. The effect of halothane on spontaneous activity was also studied. None of the neuromuscular blocking agents was observed to alter either the spontaneous contraction of myometrium strips or the contractions induced by oxytocin. Halothane abolished all spontaneous activity of human gravid myometrium strips. None of the *in-vitro* effects of the neuromuscular blocking agents appeared to contraindicate their use during anesthetic management of vaginal delivery or caesarean section. The inhibitory effect of halothane may be desirable whenever relaxation of the gravid uterus is needed. (Reier, C. E., and Moster, W. G.: *Effects of Neuromuscular Blocking Agents on Uterine Contractions in Vitro*, *Amer. J. Obstet. Gynec.* 108: 610-614, 1970.) EDITOR'S COMMENT: A very interesting study; it is a pity that no data on the effect of halothane on oxytocin-induced contractions were obtained.