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SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HEINRY K. BEECHER, M.D.†

BOSTON

HUMAN experimentation since World War II has created some difficult problems with the increasing employment of patients as experimental subjects when it must be apparent that they would not have been available if they had been truly aware of the uses that would be made of them. Evidence is at hand that many of the patients in the examples to follow never had the risk satisfactorily explained to them, and it seems obvious that further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered as a direct result of experiments described here. There is a belief prevalent in some sophisticated circles that attention to these matters would "block progress." But, according to Pope Pius XII, "... science is not the highest value to which all other orders of values... should be subordinated."

I am aware that these are troubling charges. They have grown out of troubling practices. They can be documented, as I propose to do, by examples from leading medical schools, university hospitals, private hospitals, governmental military departments (the Army, the Navy and the Air Force), governmental institutes (the National Institutes of Health), Veterans Administration hospitals and industrial basis for the charges is broad.

I should like to affirm that American medicine, and most progress in it soundly made, there is, however, a reason for concern in areas, and I believe the type of activities mentioned do great harm in medicine soon corrected. It will certainly be charged that mention of these matters does a disservice to medicine, but not one so great, I believe, as a combination of the practices to be cited.

Experimentation in man takes place in areas: in self-experimentation; in patient volunteers and normal subjects; in therapy; and in the areas of experimentation on a patient not fit but for that, at least in theory, of patients general. The present study is limited to this category.

REASONS FOR URGENCY OF STUDY

Ethical errors are increasing not only in medicine, but in variety — for example, in the recently arising problems arising in transplantation of organs.

*From the Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital.
†Dorr Professor of Research in Anesthesia, Harvard Medical School.
There are a number of reasons why serious attention to the general problem is urgent. Of transcendent importance is the enormous and continuing increase in available funds, as shown below.

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<th>Massachusetts General Hospital</th>
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The National Institutes of Health figures based upon decade averages, including funds for construction, kindly supplied by Dr. John Sherman of National Institutes of Health.

Approximation, supplied by Mr. David C. Crockett, of Massachusetts General Hospital.

Since World War II the annual expenditure for research (in large part in man) in the Massachusetts General Hospital has increased a remarkable 17-fold. At the National Institutes of Health, the increase has been a gigantic 621-fold. This "national" rate of increase is over 36 times that of the Massachusetts General Hospital. These data, rough as they are, illustrate vast opportunities and concomitantly expanded responsibilities.

Taking into account the sound and increasing emphasis of recent years that experimentation in a must precede general application of new procedures in therapy, plus the great sums of money available, there is reason to fear that these requirements and these resources may be greater than the supply of responsible investigators. All this heightens the problems under discussion.

Medical schools and university hospitals are increasingly dominated by investigators. Every young man knows that he will never be promoted to a tenure post, to a professorship in a major medical school, unless he has proved himself as an investigator. If the ready availability of money for clinical research is added to this fact, one can see that the pressures are on ambitious young physicians.

Implementation of the recommendations of the President's Commission on Heart Disease, Cancer and Stroke means that further astronomical sums of money will become available for research in man.

In addition to the foregoing three practical points there are others that Sir Robert Platt has pointed out: a general awakening of social conscience, greater power for good or harm in new remedies, new operations and new investigative procedures, etc. was formerly the case; new methods of preventive treatment with their advantages and dangers are now applied to communities as a whole as well as to individuals, with multiplication of the possibilities for injury; medical science has shown the value of human experimentation can be in solving problems of disease and its treatment; one can therefore anticipate an increase in experimentation; the newly developed concept of clinical research as a profession (for example, clinical pharmacology) and this, of course, can lead to unfortunate separa-

**FREQUENCY OF UNETHICAL OR QUESTIONABLY ETHICAL PROCEDURES**

Nearly everyone agrees that ethical violations do occur. The practical question is, how often? A preliminary examination of the matter was based on 17 examples, which were roughly increased to 50. These 50 studies contained references to 186 further likely examples, on the average 3.7 leads per study; they are too involved from paper to paper, but this figure indicates how conveniently one can proceed in a search for such material. The data are suggestive of widespread problems, but there is need for another kind of information, which was obtained by examination of 100 consecutive human studies published in 1964, in an excellent journal; 12 of these seemed to be unethical. If only one quarter of them is truly unethical, this still indicates the existence of a serious situation. Pappworth, in England, has collected, he says, more than 500 papers based upon unethical experimentation. It is evident from such observations that unethical or questionable ethical procedures are not uncommon.

**THE PROBLEM OF CONSENT**

All so-called codes are based on the bland assumption that meaningful or informed consent is readily available for the asking. As pointed out elsewhere, this is very often not the case. Consent in any fully informed sense may not be obtainable. Nevertheless, except, possibly, in the more trivial situations, it remains a goal toward which one must strive for sociologic, ethical and clear-cut legal reasons. There is no choice in the matter.

If suitably approached, patients will accede, on the basis of trust, to any request their physician may make. At the same time, every experienced clinician investigator knows that patients will often submit to inconvenience and some discomfort, if they do not last very long, but the usual patient will never agree to jeopardize seriously his health or his life for the sake of "science."

In only 2 of the 50* examples originally compiled for this study was consent mentioned. Actually, it should be emphasized in all cases for obvious moral and legal reasons, but it would be unrealistic to place much dependence on it. In any precise sense statements regarding consent are meaningless unless one knows how fully the patient was informed of all risks, and if these are not known, that fact should also be made clear. A far more dependable safeguard than consent is the presence of a truly responsible investigator.

**EXAMPLES OF UNETHICAL OR QUESTIONABLY ETHICAL STUDIES**

These examples are not cited for the condemna-

*Reduced here to 22 for reasons of space.
tion of individuals; they are recorded to call attention to a variety of ethical problems found in experimental medicine, for it is hoped that calling attention to them will help to correct abuses present. During ten years of study of these matters it has become apparent that thoughtlessness and carelessness, not a willful disregard of the patient's rights, account for most of the cases encountered. Nonetheless, it is evident that in many of the examples presented, the investigators have risked the health or the life of their subjects. No attempt has been made to present the "worst" possible examples; rather, the aim has been to show the variety of problems encountered.

References to the examples presented are not given, for there is no intention of pointing to individuals, but rather, a wish to call attention to widespread practices. All, however, are documented to the satisfaction of the editors of the Journal.

Known Effective Treatment Withheld

**Example 1.** It is known that rheumatic fever can usually be prevented by adequate treatment of streptococcal respiratory infections by the parenteral administration of penicillin. Nevertheless, definitive treatment was withheld, and placebos were given to a group of 109 men in service, while benzathine penicillin G was given to others.

"The therapy that each patient received was determined automatically by his military serial number arranged so that two groups received penicillin than received placebos. In the small group of patients studied 2 cases of acute rheumatic fever and 1 of acute nephritis developed in the control patients, whereas these complications did not occur among those who received the benzathine penicillin G.

**Example 2.** The sulfonamides were for many years the only antibacterial drugs effective in shortening the duration of acute streptococcal pharyngitis and in reducing its supplicative complications. The investigators in this study undertook to determine if the occurrence of the serious nonsuppurative complications, rheumatic fever and acute glomerulonephritis, would be reduced by this treatment. This study was made despite the general experience that certain antibiotics, including penicillin, will prevent the development of rheumatic fever.

The subjects were a large group of hospital patients; a control group of approximately the same size, also with exudative Group A streptococcus, was included. The latter group received only nonspecific therapy (no sulfadiazine). The total group denied the effective penicillin comprised over 500 men.

Rheumatic fever was diagnosed in 5.4 per cent of those treated with sulfadiazine. In the control group rheumatic fever developed in 4.2 per cent.

In reference to this study a medical officer stated in writing that the subjects were not informed, did not consent and were not aware that they had been involved in an experiment, and yet admittedly 25 acquired rheumatic fever. According to this same medical officer more than 70 who had had known definitive treatment withheld were on the ward with rheumatic fever when he was there.

**Example 3.** This involved a study of the relapse rate in typhoid fever treated in two ways. In an earlier study by the present investigators chloramphenicol had been recognized as an effective treatment for typhoid fever, being attended by half the mortality that was experienced when this agent was not used. Others had made the same observations, indicating that to withhold this effective remedy can be a life-or-death decision. The present study was carried out to determine the relapse rate under the two methods of treatment; of 408 patients, 251 were treated with chloramphenicol, of whom 20, or 7.97 per cent, died. Symptomatic treatment was given, but chloramphenicol was withheld in 137 of 36, or 22.8 per cent, died. According to the data presented, 23 patients died in the course of this study who would not have been expected to succumb if they had received specific therapy.

**Study of Therapy**

**Example 4.** TriA (triacetyloleandomycin) was originally introduced for the treatment of infection with gram-positive organisms. Spotty evidence of hepatic dysfunction emerged, especially in children, and the present study was undertaken on 50 patients including mental defectives or juvenile delinquents who were infants of a child's center. No disease other than acne was present, the drug was given in treatment of this. The ages of the subjects ranged from thirteen to thirty-nine years. "By the time the patients had received the drug for four weeks the high incidence of significant hepatic dysfunction ... led to the discontinuation of administration to the remainder of the group at three weeks. (However, only two weeks after the start of administration of the drug, 54 per cent of the patients showed abnormal excretion of bromsulphalein.) Eight patients with marked hepatic dysfunction were transferred to the hospital "for more intensive study." Liver biopsy was carried out on these 8 patients and repeated in 4 of them. No damage was evident. Four of these hospital patients, after their liver-function tests returned to normal limits, received a "challenge" dose of drug. Within two days hepatic dysfunction was evident in 3 of the 4 patients. In 1 patient a second challenge dose was given after the first and again led to evidence of abnormal liver function. Flocculation tests remained abnormal in some patients as long as five weeks after discontinuation of the drug.

**Physiologic Studies**

**Example 5.** In this controlled, double-blind study of the hematologic toxicity of chloramphenicol, it was recognized that chloramphenicol is "a "proleukopenic" agent" and that the treatment is a "proleukopenic" agent. The aim of the study was to determine the incidence and recovery from chlo

is a "proleukopenic" agent. The aim of the study was to determine the incidence and recovery from chloramphenicol.
pended morbidity and high mortality of aplastic anemia and that “... chloramphenicol-induced aplastic anemia can be related to dose ...” of the study was “further definition of the therapy of the drug.”

One randomly chosen patients were given 2 or 6 gm. of chloramphenicol per day; 12 patients were used. “Toxic bone-marrow depression, predominantly affecting erythropoiesis, occurred in 2 of 20 patients given 2.0 gm. and in 23 given 6 gm. of chloramphenicol daily.” The dose is recommended for routine use.

Example 6. In a study of the effect of thymectomy on the survival of skin homografts 18 children, three months to eighteen years of age, about to undergo surgery for congenital heart disease, were studied. Eleven were to have total thymectomy as part of the operation, and 7 were to serve as controls. As part of the experiment, full-thickness skin grafts from an unrelated adult donor were sewed to the chest wall in each case. (Total thymectomy was occasionally, although not usually part of coronary, cardiovascular surgery involved, and it may not greatly add to the hazards of the surgery, its eventual effects in children are known.) This work was proposed as part of a larger study of “the growth and development of children over the years.” No difference was noted in the size of the skin homograft observed in the 2 groups.

Example 7. This study of cyclopropene anesthesia and arrhythmias consisted of 31 patients. Average duration of the study was three hours: from two to four and a half hours. "Minor procedures" were carried out in all but one of the patients. Moderate to deep anesthesia, with endotracheal intubation and controlled respiration, was induced. Carbon dioxide was injected into the closed mediastinum system until cardiac arrhythmias appeared. Toxic levels of carbon dioxide were reached and maintained for considerable periods. The cyclopropane anesthesia a variety of new cardiac arrhythmias occurred. When the carbon dioxide tension was elevated above normal, paroxysmal extrasystoles were more numerous than the carbon dioxide tension was normal, ventricular arrhythmias being continuous in 1 subject for sixty minutes. (This can lead to fatal fibrillation.)

Example 8. Since the minimum blood-flow patients of the cerebral circulation are not accurately known, this study was carried out to develop "cerebral hemodynamic and metabolic changes before and during acute reductions in pressure induced by drug administration postural adjustments." Forty-four patients ages varied from the second to the tenth were involved. They included normotensive, those with essential hypertension and, at group with malignant hypertension. Fifteen had abnormal electrocardiograms. Few details about the reasons for hospitalization are given.

Signs of cerebral circulatory insufficiency, which were easily recognized, included confusion and in some cases a nonresponsible state. By alternation in the tilt of the patient "the clinical state of the subject could be changed in a matter of seconds from one of alertness to confusion, and for the remainder of the flow, the subject was maintained in the latter state." The femoral arteries were cannulized in all subjects, and the internal jugular veins in 14.

The mean arterial pressure fell in 37 subjects from 100 to 48 mm. of mercury, with signs of cerebral ischemia. "With the onset of collapse, cardiac output and right ventricular pressures decreased sharply.

Since signs of cerebral insufficiency developed without evidence of coronary insufficiency the authors concluded that "the brain may be more sensitive to acute hypotension than is the heart."

Example 9. This is a study of the adverse circulatory responses elicited by intra-abdominal maneuvers:

When the peritoneal cavity was entered, a deliberate series of maneuvers was carried out (in 6 patients) to ascertain the effective stimuli and the areas responsible for development of the expected circulatory changes. Accordingly, the surgeon rubbed localized areas of the parietal and visceral peritoneum with a small ball sponge as directly as possible. "Traction on the mesentery, pressure in the area of the celiac axis; traction on the幽门, and occlusion of the portal and inferior vena cava were the other stimuli applied."

Thirty-four of the patients were sixty years of age or older; 11 were seventy or older. In 44 patients the hypotension produced by the deliberate stimulation was "moderate to marked." The maximum fall produced by manipulation was from 200 systolic, 105 diastolic to 42 systolic, 20 diastolic; the average fall in mean pressure in 26 patients was 55 mm. of mercury.

Of the 50 patients studied, 17 showed either atrioventricular dissociation with nodal rhythm or nodal rhythm alone. A decrease in the amplitude of the T wave and, elevation or depression of the ST segment were noted in 25 cases in association with manipulation and hypotension or, at other times, in the course of anesthesia and operation. In only 1 case was the change pronounced enough to suggest myocardial ischemia. No case of myocardial infarction was noted in the group studied, although routine electrocardiograms were not taken after operation to detect silent infarcts. Two cases in which electrocardiograms were taken after operation showed T-wave and ST-segment changes that had not been present before.

These authors refer to a similar study in which more alarming electrocardiographic changes were observed. Four patients in the series sustained silent myocardial infarctions; most of their patients were undergoing gallbladder surgery because of...
associated heart disease. It can be added further that in the 34 patients referred to above as being sixty years of age or older, some doubtless had heart disease that could have made risky the maneuvers carried out. In any event, this possibility might have been a deterrent.

Example 10. Starling’s law — “that the heart output per beat is directly proportional to the diastolic filling” — was studied in 30 adult patients with atrial fibrillation and mitral stenosis sufficiently severe to require valvulotomy. “Continuous alterations of the length of a segment of left ventricular muscle were recorded simultaneously in 3 of these patients by means of a mercury-filled resistance gauge suported to the surface of the left ventricle.” Pressures in the left ventricle were determined by direct puncture simultaneously with the segment length in 13 patients and without the segment length in an additional 13 patients. Four similar anesthetized patients were studied through catheterization of the left side of the heart transectally. In all 30 patients arterial pressures were measured through the catheterized brachial artery.

Example 11. To study the sequence of ventricular contraction in human bundle-branch block, simultaneous catheterization of both ventricles was performed in 3 patients. Catheterization of the right ventricle was performed by way of the carotid sinus, which was catheterized transthorally. Pressures were produced by tapping on the epicardium of subjects with normal myocardium while they were undergoing thoracotomy. Simultaneous pressures were measured in both ventricles through needle puncture in this group.

The purpose of this study was to gain increased insight into the physiology involved.

Example 12: This investigation was carried out to examine the possible effect of vagal stimulation on cardiac arrest. The authors had in recent years transected the homolateral vagus nerve immediately below the origin of the recurrent laryngeal nerve as palliation against cough and pain in bronchogenic carcinoma. Having been impressed with the number of reports of cardiac arrest that seemed to follow vagal stimulation, they tested the effects of intrathoracic vagal stimulation during 30 of their surgical procedures, concluding, from these observations in patients under satisfactory anesthesia, that cardiac irregularities and cardiac arrest due to vagovagal reflex were less common than had previously been supposed.

Example 13. This study presented a technic for determining portal circulation time and hepatic blood flow. It involved the transcutaneous injection of the spleen and catheterization of the hepatic vein. This was carried out in 43 subjects, of whom 14 were normal; 16 had cirrhosis (varying degrees), 9 acute hepatitis, and 4 hemolytic anemia.

No mention is made of what information was divulged to the subjects, some of whom were seriously ill. This study consisted in the development of the technic, not of therapy, in the 14 normal subjects.

Studies to Improve the Understanding of Disease

Example 14. In this study of the syndrome of hepatic coma in patients with cirrhosis of the liver, certain nitrogenous substances administered to 9 patients with chronic alcoholism and advanced cirrhosis: ammonium chloride, ammonium citrate, urea or dietary protein. Patients a reaction that included mental disturbance, a “flapping tremor” and electroencephalographic changes developed. Similar signs had occurred only 1 of the patients before these substances were administered.

The first sign noted was usually clouding of consciousness. Three patients had a second or a third of administration of a nitrogenous substance without the same result. It was concluded that marked reaction between this reaction and impending hepatic coma applied that the administration of these nitrogenous substances to patients with cirrhosis may be hazard.

Example 15. The relation of the effects of ammonia to liver disease was investigated in normal subjects, 6 with acute virus hepatitis with cirrhosis, and 8 miscellaneous patients. These patients had no noticeable changes with either hepatic cirrhosis or virus hepatitis.

The hepatic and renal veins were catheterized, ammonium chloride was administered. After this a tremor that lasted for three minutes developed in 1 patient. When ammonium was ingested by 4 cirrhotic patients the mental confusion and the symptoms were similar during the test. The same thing was true in another group.

Example 16. This study was directly directed at determining the period of infectivity of infective hepatitis. Artificial induction of hepatitis was carried out in an institution for mentally defective children in which a mild form of hepatitis was endemic. The parents gave consent for the intramuscular or oral administration of the virus, but this was said regarding what was told them concerning the appreciable hazards involved.

A resolution adopted by the World Medical Association states explicitly: “Under no circumstance a doctor permitted to do anything which weaken the physical or mental resistance of the patient being except from strictly therapeutic indications imposed on the patient.” There is no right to risk an innocent person for the benefit of others.

Example 17. Live cancer cells were injected into 22 human subjects as part of a study of inoculation therapy. According to a recent review, the (hospitalized patients) were “merely” receiving “some cells”; “cancer was entirely omitted. . . .

Example 18. Melanoma was transplanted to the skin of the daughter to study the treatment of cancer of the cervix. The patient died of the disease, and a graft was transplanted into her daughter’s cervix. It was attempted twice the primary excision. The daughter’s cervix was normal for a hundred years, and the melanoma was the only abnormal tissue. She died of lung cancer, 20 years later. She died of lung cancer, 20 years later. She died of lung cancer, 20 years later.

Technical Study

Example 19. The administration of dopamine was done over a period of the twenty-fourth hour. She died of lung cancer, 20 years later. She died of lung cancer, 20 years later.

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SUMMARY AND CONCLUSIONS

The ethical approach to experimentation in man has several components; two are more important than the others, the first being informed consent. The difficulty of obtaining this is discussed in detail. But it is absolutely essential to strive for it for moral, scientific, and legal reasons. The statement that informed consent has little meaning is not only wrong, it is misleading. It is indeed possible that what is to be undertaken and unless all information is given, a parallel can be seen in the recent Phase II action in the United States Supreme Court. It was stated there that evidence unconstitutionally obtained cannot be used in any judicial decision, no matter how important the evidence is to the ends本公司.

hazards are made clear. If these are not known, too, should be stated. In such a situation the subject at least knows that he is to be a participant in an experiment. Secondly, there is the moral safeguard provided by the presence of an investigator, informed, conscientious, compassionate, and responsible investigator.

Ordinary patients will not knowingly risk their health or their life for the sake of "science." An experienced clinician investigator knows this. Such risks are taken and a considerable number of patients are involved, it may be assumed that the formed consent has not been obtained in all.

The gain anticipated from an experiment commensurate with the risk involved.

An experiment is ethical or not at its inception—does not become ethical post hoc—ends justify means. There is no ethical distinction between ends and means.

In the publication of experimental results, it must be made unmistakably clear that the primary object of the experiment has been achieved. It is debatable whether the obtained results should be published even if the ethical comment here is justified.

REFERENCES

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MEDICAL PROGRESS

IDIOPATHIC THROMBOCYTOPENIC PURPURA (Concluded)*

MARIO BALDINI, M.D.†
PROVIDENCE, RHODE ISLAND

SYMPTOMATIC IMMUNOLOGIC THROMBOCYTOPENIC PURPURA

Association with Virus Disorders

Probably only chronic thrombocytopenic purpura is truly idiopathic. The acute form is often preceded by a "viral" infection, particularly the exanthematous infections of children, and may therefore have a clear etiology.

Viruses have been associated with thrombocytopenia in various ways. Recent studies, including those of me and my co-workers, have shown that human blood platelets contain large amounts of sialic acid (assumed to be the virus) that myxoviruses are adsorbed to and elbowed blood platelets. In this process of adsorbed blood platelets undergo severe physical changes and become agglutinated. These experiments strongly suggest that blood platelets may serve as carriers of viruses in the circulation that in the process, they may become damaged and partially destroyed. The thrombocytopenic occasion is observed during the acute phase of infection could be related to the viremia to the capacity of the virus to alter the platelets. It is also possible that production of platelets is altered in these circumstances since...