Discussion

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My discussion is about three committees on which I serve at the University of Michigan. Perhaps this will help to establish some principles with a few specific examples. The committee meetings must keep a certain confidentiality, which is easily solved here by omitting individuals' and investigators' names. Also, I'll confine myself to classes of compound rather than specific ones.

Students as a group do not participate in all these committee actions, and this introduces certain difficulties. These students, whom we are expected to teach, have strong, diverse opinions. If we get one student on a committee, it may be good for his political standing with his fellows, but it doesn't teach the whole class. I wish the whole class were involved in committee discussions, but then we would destroy the confidentiality. So, much of the *teaching* aspect so important in these committee discussions is not available to the students.

Regarding the first committee with which I have worked, the Radioisotope Committee, a primary principle is that the pharmacology of a compound has a great deal to do with decisions as to what is permissible in investigations. In 1947, this type of committee might be considered the grandfather of the peer review committees. By 1952, the Atomic Energy Commission had formal arrangements for regulating the use of radioisotopes in human beings, and radiation policy committees were set up in the universities, with subcommittees on human use. Our committee in Michigan started in 1952.

Table I shows a problem with an investigational drug using tritium. If 100 microcuries of tritium is given in the form of water, the whole body dose is only about 8 millirads, which is about the dosage one gets from cosmic radiation in about one month in most parts of the United States. In general it isn't a very high dose. On the other hand, along came an application to use a congener of cytarabine because studies in animals didn't clearly indicate how the human being would dispose of it. A company wanted to investigate this in human beings, using 100 microcuries of tritiated cytarabine congener, which was not used in the previous 20 protocols. This posed problems. The drug is not like other tritiated compounds, for the genetic material would take it up. It is very difficult to estimate how much this use would increase the radiation dose to the genetic material. Estimates ranged from 15- to 1,000-fold increased biologic effectiveness in this instance. We decided it just could not be done except in people who could, for some reason, eventually benefit by it. This was an antiviral compound and certain people with malignant diseases would be in serious trouble if they contracted a viral disease; this particular compound might prove to be very helpful to them. Therefore, it

might be justifiable in those instances to ask them to participate as research subjects. In fact, this study was not initiated at Michigan after all the discussions were completed.

Table II illustrates another principle, namely, that in certain circumstances you can proceed with an investigational tool on the basis that the subject has little to gain but nothing to lose. Consider first objections to use of ^{131}I in the form of radioiodinated serum albumin intrathecally. From the suggested 100 μc of this compound (^{131}I-iodoalbumin), the whole body dose would be in the range of 30 to 150 millirads with much higher local dose.

If one wanted to give 50 millicuries of an ^{131}I-chloroquine analogue the whole body dose would be almost 100 rads at the highest—a big whole body dose. Why was this permitted? Because the people in whom the investigators wished to use this analogue had disseminated malignant melanoma, no other therapy was available and this was an attempt to treat them; in other words, it was intended for their own immediate good.

Now, there were questions as to whether it would help them, for melanoma is not a radiosensitive tumor (relatively) and, second, even in the usual black melanoma, not all cells are melanotic. Therefore, it was questionable whether these people would really get a cure from malignant melanoma or get tremendous benefit. On the other hand, it was considered unethical to refuse them this possibility. One could sit and watch them die or let this investigator try to do something for them. The choice was obvious.

There are two ways to look at this: We have to consider the pharmacology of the compound and use clinical common sense as to what can be allowed and what cannot. Thus, either we can find measures that are of such low risk that we don't have to think a great deal about whether the investigation is likely to help or not, or we find situations in which the patient has so little to lose that it would be wrong to deny him this one chance in a thousand of being helped. However, most of the time it isn't that simple and one has to make other decisions. We come now to the third principle, in situations involving the second review committee.

Table I. *The case of the dangerous radioisotope*

Prior to 1970, the Subcommittee on Human Use of Radioisotopes had approved 20 protocols using tritium in doses ranging from 2μc to 2mc.
Application No. 21 requested the use of 100 μc to study the metabolic disposition of a congener of cytarabine

Table II. *The "hopeless" case*

The Subcommittee on Human Use of Radioisotopes restricted the use of ^{131}I-iodoalbumin (intrathecal) to special diagnostic problems (e.g., CSF leaks), even though the established whole body dose from the administered 100μc $\cong$ 30 to 150 mrads. The spinal cord might receive a local dose as high as 40 to 60 rads
Yet this Subcommittee approved administration of 50 mc. of an experimental ^{131}I-chloroquine analogue systemically to certain patients. Their *whole body dose* is 70 to 95 rads

By February 1966, the Surgeon General's edict, with which you are all familiar, had been issued, and by the end of March 1966, we had a standing committee that dealt with various forms of human investigation, quite apart from the Radioisotope Committee.

Table III lists some examples of cases that plagued this review committee. A study that in itself was safe might frighten the subject. The otologists were interested in obtaining audiograms to test the hearing of people who had terminal illnesses, in the event that some of them would come to autopsy. They might then be able to compare the findings in the inner ear with the audiograms. Not everyone with a terminal illness is miserable and in pain at that time. The investigators were quite careful to stay away from anyone who was in pain or would in any way be harassed

Table III. *Cases that plague review committees*

No.	*Cases*
1	Studies that are themselves safe and reasonable but may still be frightening to the subject
2	Studies that are themselves safe and reasonable but may still be embarrassing to the subject
3	Invasion of the body by indwelling catheters, etc.
4	Studies during pregnancy and delivery
5	Anesthesia

by the procedure. The patient was, of course, not told he was being studied because of his condition. While the procedure had no benefit to him, the investigators were very careful to make sure it would not affect the patient's treatment, and, since an audiogram is a painless procedure, it is the kind of thing that could be allowed rather easily. However, by the "hospital grapevine," it would eventually become known that the audiograms were being used for this purpose and would frighten the persons concerned. Therefore, we just couldn't allow the investigators to select their subjects, no matter how careful they were with the terminally ill patients.

Since it was a painless and harmless test and since the investigators were not doing this for anything except hearing research, we allowed them to do it provided they also sought out *other* people at random. Our concern was that they do nothing to frighten the subjects.

We also had to deal with situations that involved embarrassment. For example, a psychiatrist wished to do something that required a follow-up of what had been done in the past. This meant following up people who had been seen in the student health center by a psychiatrist in previous years. The questionnaire they proposed was not unreasonable and the people were not in any way coerced to answer it. We had one problem, however. Many people are sent to psychiatrists in college for one thing or another. The psychiatrist may find it to be a minor problem. Five years later, and after the person has left the college, suppose a letter arrives making reference to the fact that this person had been seen in psychiatry. Suppose his secretary or his wife opens the letter—it is like a voice out of the past!

Although there was nothing in the letter that one would find offensive, it might be opened by someone other than the rightful recipient and cause embarrassment. Therefore, we didn't think this should be allowed, even though it was a very mild request—simply a letter asking for certain follow-up information from the subject himself.

Number three in the list of problems before the review committee is much stickier. It involved investigation of hearing by a new method. It is very important to find out if a young child has normal hearing, to determine whether problems are associated with deafness or with mental retardation. Many children unfortunately are called mentally retarded even though they are very bright; the problem is with their poor hearing. In the younger age group, the proposed method of testing hearing was by evoked cochlear potential and involved putting electrodes in the middle ear. The investigators wanted to start with adults. We felt as follows: No matter how much they told the person and no matter how unequivocally he consented, we wouldn't permit puncturing the eardrum solely for research purposes, even if the subject understood exactly what was being done. Therefore, initially they had to start with people who already had punctured eardrums from previous disease or who had no eardrums.

Now, what happens when you finally decide that this is a useful method and you wish to use this in an infant? Then it will require a myringotomy for the purpose of trying to help the infant. On the other hand, the first infant in whom this is done is still an experimental subject. How does one know the first time around that this investigation will actually help the child?

The switching from adults to children is very difficult. What are the rights of a parent to commit children to investigation? Taking an example from obstetrics, what are the rights of a parent to commit a fetus to investigation? Do they have such rights? These are serious problems to deal with.

Nevertheless, we can't stop all the progress in obstetrics. In the long run, this would be to the disadvantage of pregnant women. Recently, some of us were prepared to veto a proposal to monitor the use of a prostaglandin as a method of inducing labor after the standard oxytocic hormone had failed. One investigator wanted a catheter in the uterus through the abdominal wall. We said, "Ridiculous, we can't allow a thing like that." It turned out that obstetricians in many places used that type of monitoring routinely in trying to induce labor. It can be part of medical practice to put a catheter in the uterus to monitor the progress of labor and their answer was, "Do you want to deprive a patient of an investigational drug—after the standard drug has failed—using the same protective monitoring that goes on with the standard drug?" Obviously, the answer then was "no."

As to the fifth problem, we feel that general anesthesia should not be induced routinely purely for investigational purposes. But what happens if you want to do early studies on a new anesthetic agent? Are you going to start with sick people? Are they to be the first to receive a new general anesthetic?

We had this problem in a prison study and we finally permitted short general anesthesia to be given for a few minutes as a Phase I study. It was administered by a professor of anesthesiology, with a professor of pharmacology doing the monitoring. Under these conditions we would allow it, and no adverse effects resulted. Nevertheless, we are always worried about general anesthetics.

Subject selection requires careful consideration. In my own experience, I've found four types that constitute poor selections (Table IV). People who are psychiatrically borderline are not good research subjects unless the study has to be done on psychiatrically borderline people. The first one listed was an individual who was regularly "on" all sorts of drugs on campus. He would make a very poor volunteer for a drug study, even though he'd be delighted to take any drug that we would give him.

Table IV. *The case of the poor selections*

No.	*Subjects who were poor candidates for drug studies*
1	A drug-seeking hippie
2	A "volunteer" under family pressure
3	An attorney (!)
4	A patient in danger of sudden death

The second was a so-called volunteer, but after I talked to him I discovered he was frightened and did not wish to participate in research but was doing it under family coercion. Of course, we did not use him.

Litigious persons are not good subjects. Maybe it's unfair to assume that attorneys involve *themselves* in lawsuits more than other people.

Another poor selection would be a patient in danger of sudden death, e.g., one who might have a sudden myocardial infarct, even if the study had nothing in it that could precipitate a cardiac arrest. If you think the volunteer is in such danger, he is a very poor subject to select.

A very interesting case was presented to our committee by an investigator who wanted to do endocrine studies using students as subjects. He wasn't studying contraception specifically, but he wanted to learn the effect of contraceptive drugs on certain endocrine functions. These girls were students, minors, unmarried, and they were told that they were going on contraceptives. But in the original plan they would not have been specifically told that the study would be controlled by placebo. This protocol received a fast veto (Table V).

A series of studies has been conducted, beginning in 1964, in prison units similar

Table V. *A case of poor planning*

No.	*An investigator proposed to the Committee to Study Clinical Research in Humans that he be allowed to conduct a study of oral contraceptives, using subjects who were:*
1	Unmarried
2	Minors
3	Students
4	Also to be given placebo controls

Table VI. *The case of the successful protocol review committee*

The clinical research activities at Southern Michigan State Prison in the first 5 years of operation (1964-1968) included 312 studies using 10,937 subjects

In the most recent year (1970) 64 studies, using 2,930 subjects, were conducted

No instance of death or serious injury from a study has occurred since the beginning of the program

in type to Deer Lodge in Montana. The units were established by Upjohn and Parke Davis at the Michigan State Prison in Jackson. Some statistics are given in Table VI. By using protocol review committees it has been possible to conduct a large number of studies and, as of 1970, there has not been a death or serious injury since the beginning of the program.

These are mostly Phase I studies. One advantage of having a committee meet rather regularly is that with time it becomes unnecessary to reject very many protocols. The investigators soon learn what is and is not acceptable. After a while the acrimony tends to disappear, I believe, because certain things are known to be forbidden, and these are not proposed. This is the way it is done at Southern Michigan State Prison: When an inmate is admitted to that prison he receives a notice which he can send in if he wishes. Nobody approaches him directly to ask if he wishes to be part of the drug experimentation group. Very few people volunteer initially. They wait until they have talked to other

Table VII. *Cases of change in protocol*

From August 1969 through August 1971 the Michigan Protocol Review Committee modified submitted protocols for Phase I studies as follows:

Modifications	*Instances*
Improved monitoring of subjects	34
Exclusion of certain subjects	14
Improved design and logistics of study	6
Submission of additional preliminary data	3
Improved informed consent	1

Table VIII. *Improved monitoring of subjects*

Improvements	*Instances*
Amount of blood withdrawn	8
Additional liver function studies	7
Additional coagulation studies	5
Change in dose schedule	4
Electrocardiography	3
Slit lamp examination	2
Additional blood counts	2
Miscellaneous	3

prisoners to find out whether they should participate. If they do volunteer they are interviewed by the people concerned with the drug study. When the protocol is developed it has to be reviewed by a protocol review committee consisting of physicians from the University of Michigan and others in private practice in Jackson, Michigan. There is also a physician from Wayne State University, and now an attorney has been added. A few statistics from the last two years' activities of that committee are shown in Table VII.

The most common objections we have made refer to monitoring. In several instances we have insisted on closer monitoring. In Phase I studies, the most important thing is to watch the subjects carefully for signs of adverse effect from the drug, signs of disturbed function of any kind. Then one must stop the medication. There is no way to raise the dose by increments in a Phase I study without very careful monitoring of the subjects.

Table IX. *Exclusion of subjects*

Exclusion	*Reason*
Previous reaction	Vaccine to be used in the study
Previous psychosis	Steroid to be used in the study
Previous phlebitis	Steroid to be used in the study
Previous exposure	Chloramphenicol to be used in the study
Previous liver disease	Creatinine phosphokinase determinations important
Multiple allergies	High risk of sensitization
Recent trauma	Heparin to be used
Recent blood donor	Many blood samples needed
Eye disease	Long-term antilipid drug to be used
Normal VDRL	Requires LP
Cardiac abnormality	Antimalarial to be used
Abnormal ECG	CO exposure
Infection	Sulfonamide to be used
Gynecomastia	Steroid to be used

Table VIII shows 34 protocols in which the monitoring was modified. The biggest problem was that the investigators might take too much blood. In a pharmacokinetic study, blood is taken serially and if one adds up the total amount, one may end by taking more blood than one would from a blood donor. This problem is now controlled by careful limitation of the amount of blood withdrawn. These people are also given iron supplementation where indicated (Table VIII).

Another aspect of a study is the exclusion of certain subjects. In one study the investigators wanted to obtain spinal fluid. It was necessary to explain what a spinal tap was; nevertheless, we were reluctant to approve it, as it represented invasion of the body. On the other hand, in a prison there may be many people who need lumbar punctures because of a positive serologic test for syphilis. Therefore these people could be available and they would themselves benefit from the procedure (Table IX).

Summary

In summary, this was an attempt to set down some principles based on the work of three committees on which I have served. By means of some practical examples I have tried to suggest a few guidelines for conducting research with volunteers. I believe that such principles, illustrated by practical examples, are useful to investigators and aid in the guidance of committees in their function as review bodies.

Any set of guidelines should be just that; if they are too rigid they are likely to lead to serious difficulty. If rigid guidelines are put into law and interpreted not only by various federal agencies at the top level but by middle bureaucrats and lower echelon bureaucrats, bad mistakes are likely. A truism in this work is the need for individualizing each case to avoid the risk of mistakes arising from strict and inflexible application of the guidelines. It is my hope that we can keep guidelines as aids for peer review groups in making individual decisions, rather than as rigid rules.