Only Congress can change Congress, and with things as they are, this means that the congressional elders would have to decide to diminish their own power. It is a truism that the longer a congressman serves, the more influential he grows and the less critical of the institution he becomes. The political scientists have a word for this process of indoctrination and conditioning of the individual—"socialization." And what it means in Congress for reform is that the men who count honestly feel that the critics just don't understand.—JOHN WALSH

Human Experimentation: Cancer Studies at Sloan-Kettering Stir Public Debate on Medical Ethics

New York, N.Y. For about a decade a team of cancer researchers led by Chester M. Southam of the Sloan-Kettering Institute for Cancer Research has been injecting human beings with live cancer cells in order to study human immunity to cancer. Their work has been widely regarded as among the most promising of all lines of research on cancer, and it has been far from secretive. As results accumulated, at least 18 reports were published in well-circulated scientific journals. The contributing scientists have also described their activities in lectures and symposiums held round the world.

Two weeks ago the work became the focus of an internecine battle in the Jewish Chronic Disease Hospital in Brooklyn, N.Y., which was cooperating with Sloan-Kettering on one stage of the research, and sensational charges concerning the conduct of the experiments were dramatized by the New York papers. The most spectacular allegation is that some of the experiments have been performed without the informed consent of the participants. The charges have set off an investigation by the state Board of Education, a legal joust over hospital records in the State Supreme Court, and, at least in New York, the hottest public debate on medical ethics since the Nuremberg trials of Nazi physicians—an analogy not lost on some of the city's more flamboyant journals. Insofar as they can be separated from the insinuations, the facts in the imbroglio are these.

Between February 1954 and July 1956, in their first human experiments in cancer immunology, Southam's group worked with 14 patients in Memorial Hospital with advanced incurable cancer, inoculating them with cancer cells different from their own. According to a Sloan-Kettering spokesman, these patients knew that they were receiving cancer cells, understood the reasons for the experimentation, and consented to it orally. It was discovered that the implanted cancer cells did grow in the cancer patients and produced small nodules which, if they were not excised, continued to grow 4 to 6 weeks, then regressed spontaneously and completely (*Science*, 25 Jan. 1957).

The implanted cancer cells appeared to have no effect on the course of the patients' own disease. There were no untoward effects of these experiments on the patients, nor had there been any theoretical reason to expect any. There were, however, three complications, reports of which have been excavated to promote current accusations that the later stages of the work involved great risks of "causing cancer" (this is denied by the researchers). Two of the patients, suffering from what was thought to be incurable cancer at the time of the implantations, died before the anticipated regressions had occurred. In four patients cancer growth recurred at the site of the implants, after excision of the nodules. And in one patient the implanted cells were found to have metastasized.

At about the same time the researchers had established that implants of normal cells did not grow in cancer patients. It was also found that the cancer patients did not in general lack immune reactions to other diseases. To test the theory that cancer patients lacked immunity to the cancer cell implants, it was then necessary to demonstrate that the effects observed with cancer patients did not also occur in healthy individuals. At this stage the doctors faced a choice that has confronted researchers since the beginning of experimental medicine: Should they use themselves as subjects?

It is not very clear how this dilemma was resolved. Sloan-Kettering last week issued a press release stating that the researchers did inject themselves with cancer cells and established the safety of the procedure, before trying out larger-scale experiments at the Ohio State Penitentiary. Southam, however, who ought to know, said in an interview with *Science* that, although there was no theoretical likelihood that the injections would produce cancer, he had nonetheless been unwilling to inject himself, or his colleagues, when there was a group of normal volunteers at the Ohio Penitentiary fully informed about the experiment and its possible risks and nonetheless eager to take part in it. "I would not have hesitated," Southam said, "if it would have served a useful purpose. But," he continued, "to me it seemed like false heroism, like the old question whether the General should march behind or in front of his troops. I do not regard myself as indispensable—if I were not doing this work someone else would be—and I did not regard the experiment as dangerous. But, let's face it, there are relatively few skilled cancer researchers, and it seemed stupid to take even the little risk."

From 100 fully informed volunteers at Ohio ("The inmates at Ohio have a terrific reputation for enthusiastic participation in medical research," Southam said), 14 men were chosen. Their explicit, detailed consent was obtained in writing. In May 1956, what was presumably the first injection of live cancer cells into healthy human beings took place. As anticipated, the healthy subjects did in fact reject the cancer cells, and at a rapid rate. Four weeks after implantation the nodules had completely regressed, and there were no recurrences. Since the first trials, a variety of experimental refinements have been pursued at Ohio, and although it was reasonably certain that the tests involved no risks, in every case experimentation on healthy volunteers has been accompanied by informed, written consent.

At the same time, however, research was also proceeding on individuals who were not healthy, first on cancer patients at Memorial Hospital, later on patients with other advanced diseases at the Jewish Chronic Disease Hospital in Brooklyn. Although all the facts are not yet in, it is at least clear that the precedents of frankness and written consent established with the healthy volunteers were not followed with either group of hospitalized patients. Since the circumstances of the experimentation at the two institutions diverge considerably, it is necessary to look at the two separately.

The Work at Sloan-Kettering

At Sloan-Kettering, studies on the rate of rejection of implanted cancer cells in patients with advanced cancer proceeded steadily after the initial re-

search. Somewhere along the line, however, the practice of fully explaining the experiment to the patients and obtaining their informed consent was replaced by the practice of obtaining oral assent only to a vague description of the procedures, in which the word *cancer* was entirely omitted and patients were merely told that they would be receiving "some cells."

Does this constitute consent? Does it adequately protect the patients? the institution? the researchers? Sloan-Kettering evidently no longer thinks so, and it has just announced that henceforth it will insist on written consent for all such work. Southam, however, who is primarily responsible for the procedures followed, is exceedingly reluctant to see them changed, despite considerable public pressure and criticism from some fellow medical researchers.

"We stopped telling them they were getting living cancer cells when it was well established that there was no risk," Southam said last week. "We *knew* that rejection would occur; the only thing we didn't know was *when*. This has caused some trouble because rejection did not always occur before the death of the already-terminal patient; but I know, though I can't prove, that rejection would have occurred. Only in very advanced cases is there even the smallest chance of the cells' growing. All I can say is that within any reasonable definition of the words 'no risk' there was no risk.

"The reason we did not tell them," Southam continued, "was for their sake, not ours. The cancer patients at Memorial Hospital seem to develop a bizarre, defensive reaction against the knowledge they have cancer, and I am not sure I would not develop it too. To inform them more explicitly about the experiment, this defense would have to be broken down. To what purpose? I told them that they would be getting some cells, and I described what would happen, but—since I believed that there was no risk to them under the circumstances—to tell them the nature of the thing injected seemed irrelevant.

"If as a result of this uproar," Southam concluded, "either the law or the hospital regulations are changed to require more explicit definitions, of course I will comply. I would be perfectly willing to utilize a complicated scientific description, or even a commonly understood term such as 'neoplastic cells.' But I do not see why I should be obliged to confront the patients with the word 'cancer.' "

Southam's position, however controversial, was arrived at after a good deal of careful, sincere consideration. However, at the Jewish Chronic Disease Hospital, officials have been less willing to explain their policies and illuminate their motivations. "We simply followed the pattern established by Sloan-Kettering," hospital director Solomon Siegel said last week. But was "the Sloan-Kettering pattern" relevant to the Brooklyn institution?

What Happened in Brooklyn?

By the summer of 1963 it was well established that normal subjects rejected implanted cancer cells far more readily than patients with advanced cancer. What remained to be conclusively demonstrated was that the apparent absence of immunity noted in the cancer patients was in fact attributable to cancer, and not simply to the general debility that accompanies any severe, chronic illness.

Since all patients at Memorial Hospital have cancer, they were not suitable for this stage of the research. Therefore, Southam arranged with Emanuel E. Mandel, research director of the Jewish Chronic Disease Hospital, to conduct the experiment there. The experimental material was prepared by Southam and his associates, and they went into the hospital to observe the course of the experiment. The actual conduct of the experiment, however, was left to Mandel and a hospital physician under his direction, who last July administered the cancer cells to 22 patients. Last week, it was announced that the diseased patients had rejected the cancer implants just as promptly as healthy subjects do.

In August, however, three physicians resigned from the Jewish Chronic Disease Hospital, allegedly in protest over the way the experiment had been conducted. When an ad hoc medical grievance committee, convened by the hospital to investigate their charges, found no irregularities and instead commended the research, the physicians (who have not been publicly identified) are reported to have taken their complaints to William A. Hyman, a New York lawyer who is also one of the hospital's directors. Hyman was refused access to the patients' records, and he protested to the Board of Directors. The Board voted to endorse the grievance committee report. And Hyman, calling the procedures a "whitewash," took his story to the Brooklyn Supreme Court (and the New York newspapers), making formal application to obtain access to the relevant records.

"The 22 patients," Hyman said in an interview with *Science* last week, "were between 43 and 83 years old. All were sick. They were not informed that they were being given live cancer cells, and did not consent to it. Some of the patients were not even capable of giving consent: several were senile, some spoke only Yiddish, and one was deaf. Four of the participants in the experiment are now dead." As to the alleged safety of the experiments, Hyman points out that no one could say for sure that they would have no adverse effects on the patients' own illnesses. "If they knew that the tests would be harmless," Hyman asked, "why would they have had to do them?"

How accurate are Hyman's charges that the patients were neither adequately informed nor competent to give their consent? The details will not be known unless a court orders opening of hospital records, and perhaps not even then. (Records from both the Chronic Disease Hospital and Sloan-Kettering are also being solicited by the New York State Board of Education's Division of Professional Conduct, which is investigating whether any of the physicians involved have violated professional standards. If they have, the Board, which licenses professional personnel, could take disciplinary action such as censure or suspension of licenses. There is some question, however, whether hospital records may legally be disclosed, and the inquiry and subsequent action of the Board may have to proceed without them.)

But whether or not any of the charges is ever explicitly substantiated, enough has been learned to suggest that Hyman's allegations are not entirely fanciful. It is now established that the Brooklyn hospital did not tell the patients that they were receiving cancer cell injections, and that they were not asked for written consent. Hospital director Siegel, like spokesmen for Sloan-Kettering, asserts that the patients were told they were receiving "some cells," and that they gave oral consent. But in this case, did not the greater uncertainty of the effects of the cancer implants on the chronically ill subjects warrant an even more scrupulous attention to the facts presented them? And did the patients, even had they

been given all the facts, have unimpaired ability to make an intelligent, voluntary judgment about their participation? The arguments of the Sloan-Kettering researchers—that the safety of their experiments on terminal cancer patients was assured, and that the patients had a unique horror of the word *cancer*—do not seem easily transferable to the situation in Brooklyn.

An Ethical Wilderness?

A myriad of questions emerges from the New York case, and one at least demands attention. Are there adequate ethical guideposts for medical research on human subjects? The AMA and the Public Health Service adhere in essence to the principles enunciated by the Nuremberg Tribunal; and the researcher is subject also to a general cultural insistence on humane treatment of human beings. But these ethical codes do not provide much guidance for specific situations; they are not legally binding on the researcher, nor do they offer him a secure legal backstop for his actions. In the realm of law there is only the negative injunction developed in connection with the doctor-patient relationship—that the physician experiments at his own peril —and this can offer the researcher scant comfort. It appears that, when confronting the ethical dilemmas that must accompany each phase of experimentation on human beings, the researcher must rely to a large extent on his own judgment. The absence of legal guidance for these delicate situations raises two questions: Is it safe to be a researcher? Is it safe to be a patient?

Although no lawsuits are known to have grown out of the disclosures in New York, it is not hard to see that aroused families of participants in the experiment could take their grievances to court. Who would be the defendant —the researcher, who is allowed considerable discretion, or the institution that pays the bills? Would a court support the scientist's definition of "no risk"? Would it support his right to withhold information from patients for purposes entirely apart from the patient's own therapy? Even a written consent does not, according to NIH's legal counsel, have a secure legal status. But it could do the researcher no harm to have one in his pocket.

But if the researchers appear vulnerable, the hospitalized patients appear even more so. What justifies the rather marked distinction made between the treatment of volunteer subjects at the Ohio Penitentiary and that of the patients at the two New York hospitals?

Although in a prison context the hope of "time off" might be considered a qualifying factor, it appears safe to say that the element of coercion was absent and the prisoners chose freely to participate. A story about the experiment appeared in the prison newspaper; 100 men volunteered; and the required number were chosen. The participation of the hospital patients was brought about in a different fashion. Presumably they too were free to refuse to cooperate. But they had been pre-selected for special characteristics essential to the research, they were approached individually by persons in positions of authority in the hospitals, and they were shielded from full knowledge of the facts.

How typical is this of research on hospitalized patients? The New York *Times* reported that many local researchers took a negative view of the practices, which suggests that they are at least not universal. But at the Clinical Center of the National Institutes of Health, for example, where patients are chosen for their relevance to research projects, the very presence of the patient is taken to indicate his tacit consent. The releases obtained for research involving patients are not nearly as detailed as the releases obtained for normal volunteers.

The Food and Drug Administration's recent regulations on patient consent to drug experimentation have generated a good deal of discussion on experimental ethics, and the events in New York are sure to promote more. For this, researchers, administrators, and patients alike should only be thankful. It is not easy to weigh the well-being of the experimental subject against the need to promote medical knowledge, and many of the questions may have no clearcut answers. But the situation at present appears rather perilous for everyone.—ELINOR LANGER

The Nuremberg Code

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