SIR.-You have referred to the work of Krugman and his colleagues at the Willowbrook State School in three editorials. In the first article the work was cited as a notable study of hepatitis and a model for this type of investigation. No comment was made on the righteousness of attempting to infect mentally retarded children with hepatitis for experimental purposes, in an institution where the disease was already endemic.

The second editorial again did not remark on the ethics of the study, but the third sounded a note of doubt as to the justification for extending these experiments. The reason given was that some children might have been made more susceptible to
serious hepatitis as the result of the administration of previously heated icterogenic material.

I believe that not only this last experiment, but the whole of Krugman's study, is quite unjustifiable, whatever the aims, and however academically or therapeutically important are the results. I am amazed that the work was published and that it has been actively supported editorially by the *Journal of the American Medical Association* and by Ingelfinger in the 1967-68 *Year Book of Medicine*. To my knowledge only the *British Journal of Hospital Medicine* has clearly stated the ethical position on these experiments and shown that it was indefensible to give potentially dangerous infected material to children, particularly those who were mentally retarded, with or without parental consent, when no benefit to the child could conceivably result.

Krugman and Giles have continued to publish the results of their study, and in a recent paper go to some length to describe their method of obtaining parental consent and list a number of influential medical boards and committees that have approved the study. They point out again that, in their opinion, their work conforms to the World Medical Association Draft Code of Ethics on Human Experimentation. They also say that hepatitis is still highly endemic in the school.

This attempted defence is irrelevant to the central issue. Is it right to perform an experiment on a normal or mentally retarded child when no benefit can result to that individual? I think that the answer is no, and that the question of parental consent is irrelevant. In my view the studies of Krugman serve only to show that there is a serious loophole in the Draft Code, which under General Principles and Definitions puts the onus of consent for experimentation on children on the parent or guardian. It is this section that is quoted by Krugman. I would class his work as "experiments conducted solely for the acquisition of knowledge," under which heading the code states that "persons retained in mental hospital or hospitals for mental defectives should not be used for human experiment." Krugman may believe that his experiments were for the benefit of his patients, meaning the individual patients used in the study. If this is his belief he has a difficult case to defend. The duty of a pediatrician in a situation such as exists at Willowbrook State School is to attempt to improve that situation, not to turn it to his advantage for experimental purposes, however lofty the aims.

Every new reference to the work of Krugman and Giles adds to its apparent ethical respectability, and in my view such references should stop, or at least be heavily qualified. The editorial attitude of *The Lancet* to the work should be reviewed and openly stated. The issue is too important to be ignored.

If Krugman and Giles are keen to continue their experiments I suggest that they invite
the parents of the children involved to participate. I wonder what the response would be.

Stephen Goldby

SIR.-Dr. Stephen Goldby's critical comments about our Willowbrook studies and our motives for conducting them were published without extending us the courtesy of replying in the same issue of *The Lancet*. Your acceptance of his criticisms without benefit of our response implies a blackout of all comment related to our studies. This decision is unfortunate because our recent studies on active and passive immunisation for the prevention of viral hepatitis, type B, have clearly demonstrated a "therapeutic effect" for the children involved. These studies have provided us with the first indication and hope that it may be possible to control hepatitis in this institution. If this aim can be achieved, it will benefit not only the children, but also their families and the employees who care for them in the school. It is unnecessary to point out the additional benefit to the worldwide populations which have been plagued by an insoluble hepatitis problem for many generations.

Dr. Joan Giles and I have been actively engaged in studies aimed to solve two infectious-disease problems in the Willowbrook State School: measles and viral hepatitis. These studies were investigated in this institution because they represented major health problems for the 5000 or more mentally retarded children who were residents. Uninformed critics have assumed or implied that we came to Willowbrook to "conduct experiments on mentally retarded children."

The results of our Willowbrook studies with the experimental live attenuated measles vaccine developed by Enders and his colleagues are well documented in the medical literature. As early as 1960 we demonstrated the protective effect of this vaccine during the course of an epidemic. Prior to licensure of the vaccine in 1963 epidemics occurred at two-year intervals in this institution. During the 1960 epidemic there were more than 600 cases of measles and 60 deaths. In the wake of our ongoing measles vaccine programme, measles has been eradicated as a disease in the Willowbrook State School. We have not had a single case of measles since 1963. In this regard the children at the Willowbrook State School have been more fortunate than unimmunised children in Oxford, England, other areas in Great Britain, as well as certain groups of children in the United States and other parts of the world.

The background of our hepatitis studies at Willowbrook has been described in detail in various publications. Viral hepatitis is so prevalent that newly admitted susceptible children become infected within 6 to 12 months after entry in the institution. These children are a source of infection for the personnel who care for them and for their families if they visit with them. We were convinced that the solution of the hepatitis problem in this institution was dependent on the acquisition of new knowledge leading to the development of an effective immunising agent. The achievements with
smallpox, diphtheria, poliomyelitis, and more recently measles represent dramatic illustrations of this approach.

It is well known that viral hepatitis in children is milder and more benign than the same disease in adults. Experience has revealed that hepatitis in institutionalised, mentally retarded children is also mild, in contrast with measles, which is a more severe disease when it occurs in institutional epidemics involving the mentally retarded. Our proposal to expose a small number of newly admitted children to the Willowbrook strains of hepatitis virus was justified in our opinion for the following reasons: (1) they were bound to be exposed to the same strains under the natural conditions existing in the institution; (2) they would be admitted to a special, well-equipped, and well-staffed unit where they would be isolated from exposure to other infectious diseases which were prevalent in the institution-namely, shigellosis, parasitic infections, and respiratory infections—thus, their exposure in the hepatitis unit would be associated with less risk than the type of institutional exposure where multiple infections could occur; (3) they were likely to have a subclinical infection followed by immunity to the particular hepatitis virus; and (4) only children with parents who gave informed consent would be included.

The statement by Dr. Goldby accusing us of conducting experiments exclusively for the acquisition of knowledge with no benefit for the children cannot be supported by the true facts.

*Saul Krugman*

Sir.-The experiments at Willowbrook raise two important issues: What constitutes valid consent, and do ends justify means? English law definitely forbids experimentation on children, even if both parents consent, unless done specifically in the interests of each individual child. Perhaps in the U.S.A. the law is not so clear-cut. According to Beecher, the parents of the children at Willowbrook were informed that, because of overcrowding, the institution was to be closed; but only a week or two later they were told that there would be vacancies in the "hepatitis unit" for children whose parents allowed them to form part of the hepatitis research study. Such consent, ethically if not legally, is invalid because of its element of coercion, some parents being desperately anxious to institutionalise their mentally defective children. Moreover, obtaining consent after talking to parents in groups, as described by Krugman, is extremely unsatisfactory because even a single enthusiast can sway the diffident who do not wish to appear churlish in front of their fellow citizens.
Do ends justify the means? Krugman maintains that any newly admitted children would inevitably have contracted infective hepatitis, which was rife in the hospital. But this ignores the statement by the head of the State Department of Mental Hygiene that, during the major part of the 15 years these experiments have been conducted, a gammaglobulin inoculation programme had already resulted in over an 80 percent reduction of that disease in that hospital. Krugman and Pasamanick claim that subsequent therapeutic effects justify these experiments. This attitude is frequently adopted by experimenters and enthusiastic medical writers who wish us to forget completely how results are obtained but instead enjoy any benefits that may accrue. Immunisation was not the purpose of these Willowbrook experiments but merely a by-product that incidentally proved beneficial to the victims. Any experiment is ethical or not at its inception, and does not become so because it achieved some measure of success in extending the frontiers of medicine. I particularly object strongly to the views of Willey, "... risk being assumed by the subjects of the experimentation balanced against the potential benefit to the subjects and [Willey's italics] to society in general." I believe that experimental physicians never have the right to select martyrs for society. Every human being has the right to be treated with decency, and that right must always supersede every consideration of what may benefit mankind, what may advance medical science, what may contribute to public welfare. No doctor is ever justified in placing society or science first and his obligation to patients second. Any claim to act for the good of society should be regarded with distaste because it may be merely a highflown expression to cloak outrageous acts.

M. H. Pappworth

SIR.-I am astonished at the unquestioning way in which The Lancet has accepted the intemperate position taken by Dr. Stephen Goldby concerning the experimental studies of Krugman and Giles on hepatitis at the Willowbrook State School. These investigators have repeatedly explained for over a decade that natural hepatitis infection occurs sooner or later in virtually 100% of the patients admitted to Willowbrook, and that it is better for the patient to have a known, timed, controlled infection than an untimed, uncontrolled one. Moreover, the wisdom and human justification of these studies have been repeatedly and carefully examined and verified by a number of very distinguished, able individuals who are respected leaders in the making of such decisions.

The real issue is: Is it not proper and ethical to carry out experiments in children, which would apparently incur no greater risk than the children were likely to run by nature, in which the children generally receive better medical care when artificially infected than if they had been naturally infected, and in which the parents as well as the physician feel that a significant contribution to the future well-being of similar children is likely to result from the studies? It is true, to be sure, that the W.M.A. code
says, "Children in institutions and not under the care of relatives should not be the subjects of human experiments." But this unqualified *obiter dictum* may represent merely the well-known inability of committees to think a problem through. However, it has been thought through by Sir Austin Bradford Hill, who has pointed out the unfortunate effects for these very children that would have resulted, were such a code to have been applied over the years.

*Geoffrey Edsall*

Paul Ramsey : Judgment on Willowbrook

In 1958 and 1959 the *New England Journal of Medicine* reported a series of experiments performed upon patients and new admittees to the Willowbrook State School, a home for retarded children in Staten Island, New York.' These experiments were described as "an attempt to control the high prevalence of infectious hepatitis in an institution for mentally defective patients." The experiments were said to be justified because, under conditions of an existing controlled outbreak of hepatitis in the institution, "knowledge obtained from a series of suitable studies could well lead to its control." In actuality, the experiments were designed to duplicate and confirm the efficacy of gamma globulin in immunization against hepatitis, to develop and improve or improve upon that inoculum, and to learn more about infectious hepatitis in general.

The experiments were justified-doubtless, after a great deal of soul searching-for the following reasons: there was a smoldering epidemic throughout the institution and "it was apparent that most of the patients at Willowbrook were naturally exposed to hepatitis virus"; infectious hepatitis is a much milder disease in children; the strain at Willowbrook was especially mild; only the strain or strains of the virus already disseminated at Willowbrook were used; and only those small and incompetent patients whose parents gave consent were used.

The patient population at Willowbrook was 4478, growing at a rate of one patient a day over a three-year span, or from 10 to 15 new admissions per week. In the first trial the existing population was divided into two groups: one group served as uninoculated controls, and the other group was inoculated with 0.01 ml. of gamma globulin per pound of body weight. Then for a second trial new admittees and those left uninoculated before were again divided: one group served as uninoculated
controls and the other was inoculated with 0.06 ml. of gamma globulin per pound of body weight. This proved that Stokes et al. had correctly demonstrated that the larger amount would give significant immunity for up to seven or eight months.

Serious ethical questions may be raised about the trials so far described. No mention is made of any attempt to enlist the adult personnel of the institution, numbering nearly 1,000 including nearly 600 attendants on ward duty, and new additions to the staff, in these studies whose excusing reason was that almost everyone was "naturally" exposed to the Willowbrook virus. Nothing requires that major research into the natural history of hepatitis be first undertaken in children. Experiments have been carried out in the military and with prisoners as subjects. There have been fatalities from the experiments; but surely in all these cases the consent of the volunteers was as valid or better than the proxy consent of these children's "representatives." There would have been no question of the understanding consent that might have been given by the adult personnel at Willowbrook, if significant benefits were expected from studying that virus.

Second, nothing is said that would warrant withholding an inoculation of some degree of known efficacy from part of the population, or for withholding in the first trial less than the full amount of gamma globulin that had served to immunize in previous tests, except the need to test, confirm, and improve the inoculum. That, of course, was a desirable goal; but it does not seem possible to warrant withholding gamma globulin for the reason that is often said to justify controlled trials, namely, that one procedure is as likely to succeed as the other.

Third, nothing is said about attempts to control or defeat the low-grade epidemic at Willowbrook by more ordinary, if more costly and less experimental, procedures. Nor is anything said about admitting no more patients until this goal had been accomplished. This was not a massive urban hospital whose teeming population would have to be turned out into the streets, with resulting dangers to themselves and to public health, in order to sanitize the place. Instead, between 200 and 250 patients were housed in each of 18 buildings over approximately 400 acres in a semirural setting of fields, woods, and well-kept, spacious lawns. Clearly it would have been possible to secure other accommodation for new admissions away from the infection, while eradicating the infection at Willowbrook building by building. this might have cost money, and it would certainly have required astute detective work to discover the source of the infection. The doctors determined that the new patients likely were not carrying the infection upon admission, and that it did not arise from the procedures and routine inoculations given them at the time of admission. Why not go further in the search for the source of the epidemic? If this had been an orphanage for normal children or a floor of private patients, instead of a school for mentally defective children, one wonders whether the doctors would so readily have accepted the hepatitis as a "natural" occurrence and even as an opportunity for study.
The next step was to attempt to induce "passive-active immunity" by feeding the virus to patients already protected by gamma globulin. In this attempt to improve the inoculum, permission was obtained from the parents of children from 5 to 10 years of age newly admitted to Willowbrook, who were then isolated from contact with the rest of the institution. All were inoculated with gamma globulin and then divided into two groups: one served as controls while the other group of new patients were fed the Willowbrook virus, obtained from feces, in doses having 50 percent infectivity, i.e., in concentrations estimated to produce hepatitis with jaundice in half the subjects tested. Then twice the 50 percent infectivity was tried. This proved, among other things, that hepatitis has an "alimentary-tract phase" in which it can be transmitted from one person to another while still "inapparent" in the first person. This, doubtless, is exceedingly important information in learning how to control epidemics of infectious hepatitis. The second of the two articles mentioned above describes studies of the incubation period of the virus and of whether pooled serum remained infectious when aged and frozen. Still the small, mentally defective patients who were deliberately fed infectious hepatitis are described as having suffered mildly in most cases: "The liver became enlarged in the majority, occasionally a week or two before the onset of jaundice. Vomiting and anorexia usually lasted only a few days. Most of the children gained weight during the course of hepatitis."

That mild description of what happened to the children who were fed hepatitis (and who continued to be introduced into the unaltered environment of Willowbrook) is itself alarming, since it is now definitely known that cirrhosis of the liver results from infectious hepatitis more frequently than from excessive consumption of alcohol! Now, or in 1958 and 1959, no one knows what may be other serious consequences of contracting infectious hepatitis. Understanding human volunteers were then and are now needed in the study of this disease, although a South American monkey has now successfully been given a form of hepatitis, and can henceforth serve as our ally in its conquest. But not children who cannot consent knowingly. If Peace Corps workers are regularly given gamma globulin before going abroad as a guard against their contracting hepatitis, and are inoculated at intervals thereafter, it seems that this is the least we should do for mentally defective children before they "go abroad" to Willowbrook or other institutions set up for their care.

Discussions pro and con of the Willowbrook experiments that have come to my attention serve only to reinforce the ethical objections that can be raised against what was done simply from a careful analysis of the original articles reporting the research design and findings. In an address at the 1968 Ross Conference on Pediatric Research, Dr. Saul Krugman raised the question, Should vaccine trials be carried out in adult volunteers before subjecting children to similar tests? He answered this question in the negative. The reason adduced was simply that "a vaccine virus trial may be a more hazardous procedure for adults than for children." Medical researchers, of course, are required to minimize the hazards, but not by moving from consenting to unconsenting subjects. This apology clearly shows that adults and
children have become interchangeable in face of the overriding importance of obtaining the research goal. This means that the special moral claims of children for care and protection are forgotten, and especially the claims of children who are most weak and vulnerable. (Krugman's reference to the measles vaccine trials is not to the point.)

The *Medical Tribune* explains that the 16-bed isolation unit set up at Willowbrook served "to protect the study subjects from Willowbrook's other endemic diseases—such as shigellosis, measles, rubella and respiratory and parasitic infections—while exposing them to hepatitis." This presumably compensated for the infection they were given. It is not convincingly shown that the children could by no means, however costly, have been protected from the epidemic of hepatitis. The statement that Willowbrook "had endemic infectious hepatitis and a sufficiently open population so that the disease could never be quieted by exhausting the supply of susceptibles" is at best enigmatic.

Oddly, physicians defending the propriety of the Willowbrook hepatitis project soon began talking like poorly instructed "natural lawyers"! Dr. Louis Lasagna and Dr. Geoffrey Edsall, for example, find these experiments unobjectionable--both, for the reason stated by Edsall: "the children would apparently incur no greater risk than they were likely to run by nature." In any case, Edsall's example of parents consenting with a son 17 years of age for him to go to war, and society's agreements with minors that they can drive cars and hurt themselves were entirely beside the point. Dr. David D. Rutstein adheres to a stricter standard in regard to research on infectious hepatitis: "It is not ethical to use human subjects for the growth of a virus for any purpose."

The latter sweeping verdict may depend on knowledge of the effects of viruses on chromosomal difficulties, mongolism, etc., that was not available to the Willowbrook group when their researches were begun thirteen years ago. If so, this is a telling point against appeal to "no discernible risks" as the sole standard applicable to the use of children in medical experimentation. That would lend support to the proposition that we always know that there are unknown and undiscerned risks in the case of an invasion of the fortress of the body—which then can be consented to by an adult in behalf of a child only if it is in the child's behalf medically.

When asked what she told the parents of the subject-children at Willowbrook, Dr. Joan Giles replied, "I explain that there is no vaccine against infectious hepatitis. . . . I also tell them that we can modify the disease with gamma globulin but we can't provide lasting immunity without letting them get the disease." Obviously vaccines giving "lasting immunity" are not the only kinds of vaccine to be used in caring for patients.
Doubtless the studies at Willowbrook resulted in improvement in the vaccine, to the benefit of present and future patients. In September 1966, "a routine program of GG [gamma globulin] administration to every new patient at Willowbrook" was begun. This cut the incidence of icteric hepatitis 80 to 85 percent. Then follows a significant statement in the *Medical Tribune* article: "A similar reduction in the icteric form of the disease has been accomplished among the employees, who began getting routine GG earlier in the study." Not only did the research team (so far as these reports show) fail to consider and adopt the alternative that new admittees to the staff be asked to become volunteers for an investigation that might improve the vaccine against the strain of infectious hepatitis to which they as well as the children were exposed. Instead, the staff was routinely protected earlier than the inmates were! And, as we have seen, there was evidence from the beginning that gamma globulin provided at least some protection. A "modification" of the disease was still an inoculum, even if this provided no lasting immunization and had to be repeated. It is axiomatic to medical ethics that a known remedy or protection-even if not perfect or even if the best exact administration of it has not been proved—should not be withheld from individual patients. It seems to a layman that from the beginning various trials at immunization of all new admittees might have been made, and controlled observation made of their different degrees of effectiveness against "nature" at Willowbrook. This would doubtless have been a longer way round, namely, the "anecdotal" method of investigative treatment that comes off second best in comparison with controlled trials. Yet this seems to be the alternative dictated by our received medical ethics, and the only one expressive of minimal care of the primary patients themselves.

Finally, except for one episode, the obtaining of parental consent (on the premise that this is ethically valid) seems to have been very well handled. Wards of the state were not used, though by law the administrator at Willowbrook could have signed consent for them. Only new admittees whose parents were available were entered by proxy consent into the project. Explanation was made to groups of these parents, and they were given time to think about it and consult with their own family physicians. Then late in 1964 Willowbrook was closed to all new admissions because of overcrowding. What then happened can most impartially be described in the words of an article defending the Willowbrook project on medical and ethical grounds:

Parents who applied for their children to get in were sent a form letter over Dr. Hammond's signature saying that there was no space for new admissions and that their name was being put on a waiting list.

But the hepatitis program, occupying its own space in the
institution, continued to admit new patients as each new study group began. "Where do you find new admissions except by canvassing the people who have applied for admission?" Dr. Hammond asked.

So a new batch of form letters went out, saying that there were a few vacancies in the hepatitis research unit if the parents cared to consider volunteering their child for that. In some instances the second form letter apparently was received as closely as a week after the first letter arrived.

Granting-as I do not-the validity of parental consent to research upon children not in their behalf medically, what sort of consent was that? Surely, the duress upon these parents with children so defective as to require institutionalization was far greater than the duress on prisoners given tobacco or paid or promised parole for their cooperation! I grant that the timing of these events was inadvertent. Since, however, ethics is a matter of criticizing institutions and not only of exculpating or making culprits of individual men, the inadvertence does not matter. This is the strongest possible argument for saying that even if parents have the right to consent to submit the children who are directly and continuously in their care to nonbeneficial medical experimentation, this should not be the rule of practice governing institutions set up for their care.

Such use of captive populations of children for purely experimental purposes ought to be made legally impossible. My view is that this should be stopped by legal acknowledgement of the moral invalidity of parental or legal proxy consent for the child to procedures having no relation to a child's own diagnosis or treatment. If this is not done, canons of loyalty require that the rule of practice (by law, or otherwise) be that children in institutions and not directly under the care of parents or relatives should never be used in medical investigations having present pain or discomfort and unknown present and future risks to them, and promising future possible benefits only for others.

LOGIC ETHICS HISTORY METAPHYSICS EPISTEMOLOGY MIND VALUE LANGUAGE

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