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PROTECTION OF THE RIGHTS AND WELFARE OF PRISON VOLUNTEERS:
POLICIES FOLLOWED THROUGHOUT A 17-YEAR MEDICAL RESEARCH PROGRAM.

Running Title: VOLUNTEER MEDICAL RESEARCH POLICIES

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INTRODUCTION

One of the longest lived experimental programs involving the use of prison inmate volunteers in studies on reproductive physiology has just been terminated. Termination occurred because of the physical disability of the principal investigator and the subsequent decision of the state officials to discontinue all research projects in state institutions. The experiments, successfully carried on from 1956 to 1973, involved the study of the normal male reproductive system and how it is affected by exogenously administered agents. The development of an agent which would allow infertile men to become fertile and the development of male contraceptive agents were specific aims. These studies were continuous for the 17-year period (1 - 43) . During the last ten years an additional goal was added; that of determining the effect of graded doses of ionizing radiation on the function of the human testis* (16, 19, 23, 27, 31, 35, & 41)

This project began prior to close scrutiny of human volunteer procedures. The development of governmental guidelines caused many changes in the protections afforded the volunteers throughout the experimental programs.

The administrative and ethical considerations of this entire program were controversial and complex. Because it was highly successful from the viewpoints of both the volunteers and investigators, we are documenting the history of the program and the administrative details of how it was run at its conclusion. We hope that it will be a

* A series of papers arising from the completed radiation experiments is currently in preparation.

useful example to others who are working or want to work in the sensitive yet indispensable area of human research.

HISTORY

Establishment of the Program

Prior to initiation of experimental work many barriers had to be overcome. These included convincing the prison physician of the worth of the program, and, in a seminar, presenting details of the proposed study and its goals to the prison superintendent. Later a written prospectus was drawn up and again approved by the physician and superintendent. The superintendent then explained the project to the state governor and the State Board of Control. Approval was obtained from each. Subsequently 125 inmates volunteered to listen to a discussion of the project. Of these, prison authorities eliminated about half, and 25 were ultimately accepted into the program.

The written prospectus and the later discussion with inmate volunteers included both the purpose and the plan of the proposed endocrinological investigation in great detail. Briefly, the purpose was explained as being "to determine the effect of several hormonal preparations upon reproduction in the human male." The plan was that "several observations will be made on each subject before the preparation is administered, at intervals during, and after the preparation has been discontinued." The observations, also explained in great detail, included seminal fluid examination, urinary studies
1003327 (gonadotropins, 17-ketosteroids, estrogens and pregnanediol), and

testicular biopsies. The exact surgical procedure used in obtaining the testicular biopsy including recuperative procedures were listed. The method of drug administration (i.e., frequency, dosage and administration route) and possible resultant effects (infertility, impotency, etc.) were described.

The question of payment to volunteers remained unsettled for some time after the experimental program was underway. Questions were raised as to the psychological impact of payment and as to what constituted fair payment without unfair inducement to participate. It was finally decided that a payment of \$5.00 per month and \$10.00 per biopsy could be made. Half of the money was held in the volunteers' savings accounts at the prison.

It should be noted that at this early date (1956) funding agencies placed no restrictions on how studies involving participation by human volunteers were carried out**. Even then, however, it was much more difficult to become an accepted volunteer for this program than to discontinue participation. All that was necessary to discontinue was to declare intent. To become involved initially the prison administration and hospital staff had to approve. In addition the health of the volunteer had to be very good and they had to be reproductively "normal".

** Our early guidelines were based on The Nuremberg Code (44), Declaration of Helsinki. (45), Dædalus: Ethical Aspects of Experimentation with Human Subjects (46), and, as they were developed the policies incorporated into The Institutional Guide to DHEW Policy on Protection of Human Subjects (47).

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Subsequent Program Development

Subsequent management of the experimental procedures and guidelines for volunteer participation were worked out as the program developed. The aim was to achieve full protection of volunteer rights and to obtain the greatest amount of scientific data from each experiment. It was felt that the more complete the data obtained from each volunteer, the more justifiable his participation became and the less chance that additional experiments would have to be done for each project.

During 1962 a new experimental direction was investigated. It was discovered that the effects of ionizing radiation on humans were, except for the grossest information, unknown. Apart from some inadequate post-mortem studies on Japanese atomic bomb victims and a few isolated case histories from nuclear accidents, no accurate information was available on the actual reaction and dose response of the human to relatively low dose radiation exposure (8 - 600r). In fact, radiation safety limits were based on animal data. Extrapolating collected information from one species to another, while often rewarding, fails as often to be either applicable or accurate. It was felt that to gain knowledge of the precise nature of irradiation changes produced in man and the duration of an effect from any dosage administered, only man could serve as the experimental subject. Since radiation exposure is a fact of life, knowing the effect and duration of a specific radiation dosage effect on man might well dispell many of the uncertainties and consequently the fears that surround radiation exposure. It was decided that the sooner

this knowledge was determined the sooner it would be available to the scientific and medical professions and the community at large.

Once the decision to do this research was reached, careful consideration was given as to how to proceed. Several reasons were given as to why the testis should have particular attention as far as radiation research was concerned. These included the fact that the seminiferous epithelium appeared to be one of the most radio-sensitive organs. The human testis is an internal organ which happens to be external and therefore is also one of the very few organs which could be isolated and exposed to radiation without exposing the rest of the body.

Since a pool from which volunteers might come was available, the penitentiary program was considered as the source of experimental material. After approval of the prison authorities, discussion was held with the various inmates to ascertain their reaction and it was found that they were, in fact, interested in participating in such a program. When told that only those men having or wishing to be vasectomized would be accepted (to avoid any possibility of contaminating the general population with irradiation-induced mutants) the men became even more interested, regarding the free vasectomy as a benefit. The next problem to be solved was that of providing a radiation device which would give uniform exposure to the testis without causing skin burn or exposure of the rest of the body. A lead-lined box containing two X-ray tubes was built. Between the tubes a small plexiglass box was filled with scrotal temperature water. A man lying across the box lowered his testes into

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the water. Uniform doses of radiation were achieved by radiating from two directions to allow a homogeneous dosage. With this equipment exposure to graded doses of ionizing radiation was restricted to the scrotum and contents. The accuracy of delivery of this X-ray device was confirmed using physical and biological dosimetry by impartial radiation experts.

It was at this time (1963) that a research proposal was written and experimentation initiated. In order to monitor experimental activities and provide expertise for unusual problems, advisory committees were selected and meetings were held. Discussion at the first meeting in November of 1963 centered around the proper handling of the volunteers. Subsequent meetings in December 1965, March 1967 and December 1967 were primarily to discuss various aspects of the work being done. Each committee was made up of nationally prominent scientific and medical experts. The first committee specifically polled officials giving permission for this project and personally visited the penitentiary to evaluate the knowledge and consent of the inmate volunteers.

Between 1963 and 1971, 74 irradiations were performed at doses ranging from 8 to 600r. Twelve men had been vasectomized prior to imprisonment. The other 62 men were vasectomized prior to release from prison or when the program terminated. None refused vasectomy, nor where there any pre-vasectomy escapees. All volunteers were offered an opportunity to participate in the hormone administration program instead of the radiation program.

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Since the cessation of new irradiations in 1971 this program has been slowly phasing out as the volunteers regain apparent reproductive system normalcy. As of 1973, however, the entire prison experimental program was terminated due to incapacity of the principal investigator and subsequent state re-evaluation of correctional institutional involvement in experimental programs.

PROJECT ORGANIZATION

Selection of Volunteer Subjects

During the duration of experimentation within the prison, the inmates became well informed, by word of mouth, and/or observation, on most details of the experimental techniques. The following was routine procedure for any man wanting to join the research program:

1. The man heard about the project from other inmate volunteers, or most usually, his cell mate, or as a result of the fact that he happened to be a hospital worker.

2. He submitted an interview request to the investigating physician via the penitentiary hospital. Actual examples are:

" Dear Sir: I would like to talk with you as soon as possible about getting on the biopsy program. I have heard a lot about it, and I think I would like to sign up for it. Thank you."

" I request to be interviewed in regards to your research program. I am particularly interested in being sterilized. Thank you."

" I request to find out what a biopsy is as I may be interested."

" I request to talk to you about the biopsy program. I want to know what they do and so on. I am interested in doing this but don't want to give an arm or something. Thank you."

" I am doing a life sentence and due to the circumstances I would like to be accepted into your research program as soon as possible. I would also like to become involved in the radiation program. I feel that if and when I get out I'll be too old to start another family."

" I request to join your research program, as I am most interested in birth control. Respectfully."

3. The investigating physician would then explain the program to each volunteer individually and answer any questions, upon his next penitentiary visit.

4. If at this point, no problems were encountered and the volunteer was still interested he was placed on the " temporary " program.

Subsequent Volunteer Management

1. While on the " temporary " program the new volunteer collected seminal fluid once per week and had a physical examination. If the man had ever been identified as Catholic he was not accepted even on the " temporary " program until he had discussed the matter with a priest. If the priest affirmed that the man was not a Catholic he was accepted onto the program. After discussion with a priest no true Catholic returned for further interviews. Examples of written statements from the priest to the investigating physician are as follows:

" would like to have his religious preference changed from Catholic to that of No Religious Preference."

" Please be informed that is not a Baptized Catholic. Upon being admitted to this institution, he stated that he had attended Catechism for a short while and had attended Mass on various occasions, and at that time he wanted to take Correspondence Courses concerning the Catholic faith. However, he has not been Baptized or Confirmed, and since he is a Catholic By Preference, he can change his faith at any time, and will not be recognized by the Catholic Church until he is Baptized and Confirmed. Therefore you may proceed in your research knowing that he is not a Catholic. His card indication has been changed in this office from (2. Cath.) to (No Preference). Thank you."

One note should be made here. At the time an inmate enters the penitentiary he has to state a religious preference. His choice is Protestant or Catholic. The purpose for this is not entirely religious as it offers the inmate someone to intervene for him and someone who is not a " cop " with whom he can talk. Therefore it is not at all surprising to find many " changing " their religious preference when inconvenienced.

2. At the end of one month (or three seminal fluid specimens) the investigating physician again talked to the man. If the sperm counts were normal, the seminal fluid was of normal volume and consistency (occasionally a man was not accepted because his semen was too thick to count), his health was good, he followed directions and

caused no problems (disciplinary or medical) to the hospital staff, and he still wished to be on the program, he was accepted onto the " control " program. Only about one out of every ten men was accepted at this point.

3. During the three- to six-month control period, plasma samples were collected six times, seminal fluid was collected once weekly and one testicular biopsy scheduled. Prior to any collections, a consent form was explained and signed. It read as follows:

I, _____ acknowledge that _____
_____ has informed me that I may submit masturbated seminal samples, blood samples, urine samples and testicular tissue, and I hereby consent to giving such samples.

I have been informed what a testicular biopsy is and that there are certain inherent risks in such a surgical procedure. These risks include but are not limited to pain, both at the time of surgery and thereafter, and I may have internal bleeding into the scrotum. I consent to the surgery by a licensed medical doctor.

The samples are to be used in a research project which does not specifically benefit me. I consent to the publication of the results of the project with the understanding that I shall not be personally identified.

I have been given the opportunity to ask any questions about the foregoing procedure. I have been advised that I may withdraw my consent

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" This 25 year old white male, father of three children was evaluated this date for inclusion into the Program. The situation of vasectomy and irradiation was discussed and he is well aware of the circumstances and was very receptive to the program. He will be recommended for this program."

"..... was evaluated for program. He is 26 years old and still has thoughts about getting married and raising a family. He is a passive dependent person who is and quite indecisive about this program. He has only vague knowledge about what these procedures are and along with this has poor foresight and planning. Although he is fully competent his judgement regarding permanent sterilization is poor and he will quite likely regret it."

" is now 37 years old, had been married and divorced three times, has two living children and one grandchild. Although he contemplates marriage again, he has no desire for further family. He has never had psychiatric treatment and shows no significant emotional disorder. There is no psychiatric contraindication to a vasectomy."

To avoid any question about influencing their decision, the investigating physician did not personally discuss the subjects' evaluation (before or after the interview) with either the psychiatrist or priest.

4. If during the control biopsy procedure the volunteer created any disturbance or if any problems arose following the procedure, the investigating physician discussed the problems with him and decided whether he should be dropped from the program.

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5. At the end of the control period (about six months) all available data were examined for normalcy (testicular biopsy, hormone analysis, sperm count and morphology, physical condition) and the man's attitude and reliability evaluated. If all were favorable, he was considered for a specific project. The exact procedures and potential risks of that project were explained to him in great detail and he was allowed to decide if he wanted to participate in that project or would rather be in another specific program.

6. Once a man selected the project in which he wanted to participate, the proper consent forms were discussed and signed. Different forms were designed for each experiment. Examples are as follows:

DRUG ADMINISTRATION CONSENT

I, _____, have been made aware by _____, that I am to be given intramuscular injections of _____ daily for a long period of time (several months). The present purpose is to determine whether this drug alters plasma hormone levels and to discover what effect it has on the testis itself by examining semen and testicular biopsies. I am also aware that while I am receiving this drug, many blood and semen samples and several testicular biopsies will be required, and I agree to supply them.

I have been informed that the samples and information obtained from me in this study may be used as part of a research project which does not specifically benefit me. I consent to the use of the information obtained in the research project, and to the publication of that information with the understanding that I shall not be personally

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I have been given the opportunity to ask any questions about the foregoing procedure. I have been advised that I may withdraw my consent at anytime and discontinue participation in the project.

Witnessed by:

Signature

Signature

Date

Date

X-RAY CONSENT

This agreement made this _____ day of _____ 19 _____
between _____ and _____.

I hereby agree to submit to X-ray radiation exposure of my scrotum and testes. I also agree to donate urine samples, semen samples, and blood samples periodically. I further agree to submit to a surgical procedure known as a testicular biopsy, performed a number of times during the length of the experiment.

I have had explained to me what a testicular biopsy is and I have knowledge of this procedure.

I hereby agree to submit to a vasectomy operation at the completion of the experimental procedures. I know that a vasectomy operation is a tying off of the cords. I am aware that sterility may result from these procedures, although such result has not been guaranteed. I know that a sterile person is incapable of parenthood. I also know that there may be some skin burn from the radiation.

The nature and purpose of the experimental procedures, the risks involved and the possibility of complications have been fully explained

to me.

It is further understood that the said procedures are to be performed at _____ and will be performed under the direction of Dr. _____. He is authorized to utilize in the performance of these procedures the services of physicians or members of the hospital staff to the extent that he deems them qualified.

I hereby swear that all of the above statements I have read and that I fully understand the meaning of this agreement.

Signed _____

Date _____

The foregoing agreement was read, discussed and signed in my presence and in my opinion the person so signing did so freely and with full knowledge and understanding.

Signed _____

Date _____

REQUEST FOR STERILIZATION

Date _____

I hereby request that I be sterilized as I do not wish to father children in the future.

Signed _____

CONSENT FOR VASECTOMY

I hereby request and authorize Dr. _____ and whomever he may designate or assign to perform upon myself the following procedure: a vasectomy. I know that a vasectomy is "tying off the cords", and that the purpose is to produce sterilization. I know that permanent sterility will probably result from this operation, although such result has not been guaranteed. I know that a sterile person is incapable of parenthood. I have been fully informed of the risks and possible consequences involved and that unforeseen results may occur.

Signed _____

Date _____

The foregoing consent was read, discussed and signed in my presence, and in my opinion the person so signing did so freely and with full knowledge and understanding.

Witness _____

Date _____

(If married)

I concur and agree with my husband's wishes to be sterilized and give my consent to the operative procedure.

Signed _____
(Wife)

Date _____

(If not married)

I hereby swear that I do not have a wife.

Signed _____

Date _____

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If the wife did not consent, those procedures requiring vasectomy were not performed.

7. During the actual experimental program, the man could discontinue taking a drug, at any time without notice. He could also refuse a testicular biopsy at any time. If a biopsy were refused late in the project, the man would be allowed to continue collecting semen and plasma. If it were refused early in the project, the man would be dropped, although he was observed medically to insure no untoward reactions from the agent administered. Although it was not required most volunteers who discontinued participation did notify us in writing. An example follows:

" I request to be removed from the research program as it interferes with my present job assignment."

8. Volunteers who were on a project and subsequently paroled or released often returned to the penitentiary for another offense. Almost without exception they re-applied to the program.

" I would like to see about getting back on your experiment (research program). I was on it once before when I was here and had my cords tied off before I left. I was also radiated once while I was on the program. I would like to get on it if possible. Thank you."

" I request to be back on the research program for biopsies and whatever. Thank you."

When this happened, they were admitted at once to control status (The "temporary" status was eliminated because of familiarity). However, all consent forms were again gone over in detail and signed.

Occasionally a man would volunteer to continue with the projects once he was released. An example of this request follows:

" I failed to ask you the last time I seen you if you would be interested in continuing the experiments with me if I should be granted Parole. Personally I am interested in this program because of how it can help mankind. I realize how devoted you are to these experiments and wish to help you in any way I can. I know you may be reluctant to continue this program with someone who has been released from here because of the change in environment as conditions here are almost ideal. Due to my wanting to help mankind with your worthy cause I know that I can be just as faithful to you in the outside world as I try to be in here. Besides, I never would have accepted or asked to get on the program in the first place if I hadn't fully intended to go along with you until you had completely exhausted your experiments with me. Believe me, it would be an honor to know that I had helped in some way for you to achieve your ultimate goal. Thank you for this opportunity."

Unfortunately, our experimental design was such that these volunteers could not participate after release.

9. One physician involved in the research visited the penitentiary daily. If needed, he was immediately available.

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SPECIFIC POINTS ABOUT THE EXPERIMENTAL PROGRAM.

The personnel staffing the portion of the laboratory which is within the prison was a mixture of inmate technicians, non-inmate technicians and supervisory personnel. All of those staffing the laboratory indicated a great interest in the research work. The non-inmate personnel visited the primary research laboratory because of their interest. Many of the volunteers as well as the technical staff, constantly requested and read reprints of our work and instructive textbook chapters.

One specific incident indicates the sense of pride the volunteers had in this work. During a severe prison riot a few years ago, the hospital was one of the areas most damaged. The rioting inmates wanted drugs and implements which could be used as weapons. Everything which could not be used was broken and smashed. There was one exception. After the non-inmate personnel had fled the area the inmate technicians passed the word as to what belonged to the research project. In the course of the rioting and looting, nothing belonging to the project was touched. Even the drug supplies were left unopened.

There was no contact with the Parole Board on behalf of any of the volunteers. There was no way by which they could derive an earlier parole or a shorter imprisonment by participation. A rare exception was for the inmate hospital technician. Occasionally, then, a reference was requested because of the work relationship.

The scientific results from studies utilizing these volunteers have

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been extremely broad and of major importance to the medical-scientific community. Rather than attempt to summarize the major accomplishments, we refer the reader to the bibliography.

DISCUSSION

Major changes occurred throughout this 17-year period to allow this research program to continue with the approval of all observing groups. For example, at the beginning a consent form was prepared for each volunteer when he was to have a drug administered. These early "forms" merely stated that the volunteer knew he was to receive an experimental drug. Almost immediately, it was decided that more formal consent documents were needed. These were drawn up with the help of an attorney and all included a phrase stating "I agree to assume all the direct and indirect risks involved, including injuries which I may sustain as a result of, and hereby absolve from any liability." With the development of the most recent federal guidelines this phrase was eliminated from all consent forms.

It is difficult to describe or explain the communication that was developed between the investigative staff and the volunteers. However, the psychological bond that existed between them was very real and created an atmosphere that allowed the inmate to speak openly and freely about himself both physically and mentally. This was very important to the accuracy of some of the more subjective medical observations. This trust was given more freely a year or so after the

program was initiated when the volunteers realized that confidences would not be passed on to the prison hierarchy. This became extremely valuable on occasion, as was evidenced by one drug which had side effects when alcohol was imbibed. This information was given to the investigators even though the volunteers realized that they would be punished if prison officials knew alcohol had been used.

We believe several factors added to the continued deep bond between the volunteers and investigators. These include:

1. The men were treated as men not " subjects ". They were talked to and their personal feelings were known in some depth. They enjoyed coming to be interviewed by " the doctor " and came often because they wanted information on every aspect of the experimental procedure as it might affect them.

2. The investigator who did the interviews was the same person throughout the 17-year period. This allowed long-term familiarity and understanding of personalities. To have constant contact with the same person is probably more important in a prison setting than any other since the inmate is generally an expert at " conning " straight people. Therefore much time is needed to get to know the volunteer, (i.e., the long " temporary " and control portions of the program) in order to discover the volunteer's sincerity in wanting to participate.

3. Even though the volunteers were comfortable with the investigators, the investigators would not allow themselves to be used by the prisoners as go-betweens to either the prison officials or the

outside world. Since this was well understood the inmates tended to respect the investigative personnel and did not involve the experimental program in intra-penitentiary problems.

4. The inmates knew that all scientific personnel including those who never visited the penitentiary cared about every detail of the program. From time to time an inmate technician would be released from the penitentiary. When one qualified to work in the research laboratory was paroled and a position was available, he was hired. Unfortunately most of them were later returned to the penitentiary, however, when this happened the other inmates learned even more about the research project.

While the rapport between the volunteers and investigators is important, it is of equal importance to maintain the goodwill of the penitentiary and state personnel. Three major factors were involved. First, we paid wages to the inmate technicians at a level specified by the penitentiary. This prevented their already busy staff from being overworked because of our program. Secondly, we notified the hospital manager one day to two weeks before needing his cooperation in moving inmates from one area to another (for interviews, etc.) or before biopsies were to be performed. This allowed scheduling of hospital work. Thirdly, we followed any official request precisely and tried to cause no additional problems.

We believe it is very important to point out again that there were no problems with either the prison officials or volunteers at the time this program was discontinued earlier this year.

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We cannot pretend that the fear of lawsuits did not cause even more care than would have been used otherwise. One such suit would have brought about the immediate termination of the program.

Many thousands of words have been written about the ethics of using institutionalized volunteers and many well-meaning individuals agonize over informed consent. We have, perhaps, achieved a slightly different view from our years of observation of this highly successful prison research program. First, we believe that true informed consent is very difficult to achieve. These people who are together, who can discuss the procedures among themselves and who can actually observe what is happening to other participants, learn a great deal about what can happen to them. A glance at their interview requests indicates that they have extensive pre-interview knowledge. Any non-institutionalized individual taking a test drug and never seeing anyone else who has been on an experimental program has only, perhaps, one brief discussion with their doctor. Inmate volunteers in a research setting as described above are perhaps the best informed human volunteers in existence (excluding medical personnel themselves).

Although it is obvious, as argued, that these people are not free physically, they are free to make the choice of participation or non-participation. There was no benefit of better prison treatment, the monetary reward was small and they had to request to be on the program. They were not asked to participate. We believe it to be far more unsound ethically to carry out investigations utilizing non-institutionalized individuals before chromosomal dangers or reproductive changes (resulting

in possible abnormal births) have been worked out on humans who cannot cause conception because of their isolation from general society. Research involving human volunteers must be done, and it is imperative that all studies be designed and carried out with utmost care and consideration.

CONCLUSION

The development and documentation of how a highly successful prison inmate volunteer program for medical research was carried on has been presented. We concluded that the major factors allowing this program to be a success included:

1. Obtaining the trust of the volunteer.
2. Obtaining the trust of prison officials.
3. Full explanation to the volunteer in language he could understand.
4. Consistency in personnel and attitudes.
5. Openness of all information pertaining to the use of humans as research volunteers to anyone concerned with the protection of the subject's rights and welfare.
Availability of inmate volunteers for interviews by these same groups or individuals.

It is our hope that this information will offer some assistance to those currently involved in or possibly considering participation in human research programs.

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