# THE PHYSIOLOGICAL APPROACH TO FERTILITY CONTROL

Report of

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WORKING GROUP ON FERTILITY CONTROL

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## THE WORKING GROUP

Kingsley Davis, Professor of Sociology, Columbia University

William vE. Doering, Professor of Chemistry, Yale University

Clair E. Folsome, M.D., Director of Department of Obstetrics and Gynecology, Flower Fifth Avenue Hospital, New York

Alan F. Guttmacher, M.D., Director of Department of Obstetrics and Gynecology, Mt. Sinai Hospital, New York

Caryl P. Haskins, President, Haskins Laboratories, New York

Paul S. Henshaw, Director of Research, Planned Parenthood Federation

Frederick L. Hisaw, Professor of Zoology, Harvard University

Evelyn Hutchinson, Professor of Biology, Yale University

Samuel R. M. Reynolds, Carnegie Embryological Laboratories, Baltimore

Robert G. Snider, Vice President and Director of Research, The Conservation Foundation, New York

Leo Szilard, Professor of Biophysics, University of Chicago

Howard Taylor, M.D., Professor of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University

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# Chapter I

## THE PROBLEM AND ITS BACKGROUND

One of the world's major problems today is the rapid growth of population and the rise of heavy population density in areas where levels of living are low. In 1950 the estimated population of the globe was 2.4 billion; in 1920, 1.8 billion. During the thirty years between the two dates, the increase was over half a billion, or 30 per cent of what the total number was in 1920.

The locus of this unprecedented rate of increase in recent years is to be found in the underdeveloped areas. These areas are still characterized by an inefficient peasant-agricultural economy, undercapitalized, poorly organized, and extremely wasteful of human labor. So much of the manpower goes into the sheer production of food and fibres on the land that there is little left over to support urban occupations, to pay for education, and to improve technology. To distinguish such countries, we can use as a rough measure the proportion of gainfully occupied males who are engaged directly in agriculture. If more than 50 per cent are so engaged, a country can be safely placed in the underdeveloped category.*

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* This definition excludes the type of nation whose economy rests primarily on products of the land but whose farming is highly efficient. Such a country cannot have half of its occupied males in agriculture, because well-capitalized and mechanized farming requires little labor and yet produces a surplus sufficient to support a substantial labor force in secondary and tertiary industry. Argentina is a case in point. Though it depends heavily on agricultural exports, less than a third of its occupied males are engaged in agriculture, and 48 per cent of its population lives in cities of 20,000 and over. Its agriculture is highly mechanized and rationalized. The same is true of New Zealand, Denmark, Australia, and other countries with what may be called an "industrialized" agriculture. New Zealand's economy depends primarily on the export of agricultural products, yet in 1936 only 27 percent of its workers were employed in primary production and over half its population lived in cities of more than 17,000 inhabitants. See K. Davis, "Population and the Further Spread of Industrial Society," Proceedings of the American Philosophical Society, Vol. 95, No. 1 (February 1951), pp. 8-19.

On this basis it turns out that the underdeveloped, or peasant-agricultural, countries and colonies embrace, as of 1947, 74 per cent of the world's habitable area and 76 per cent of its people. The inefficiency of these countries can be seen from the fact that, for them, the average number of agriculturally-employed males per square mile of agricultural land is approximately 113, whereas it is only 32 for the advanced, or industrial, nations. In other words, the peasant-agricultural countries use far more labor on the land than do the others, and this means that there is far less surplus left over for developmental activities after the needs of the rural population have been met.

Despite their inefficiency, the underdeveloped areas are experiencing at present a very fast rate of population growth. Whereas the urban-industrial peoples generally by now have learned to control their reproduction by private means and have thus shown slackening rates of population increase, the opposite is true in agrarian Asia, Africa, Oceania, and Latin America. The latter areas are either entering or are in the midst of a very rapid phase of demographic expansion. They are also trying to raise their level of living by industrialization and the improvement of agriculture, but in many cases--e.g. India, Indonesia, Egypt, Ceylon, Formosa, and at least twenty other countries--the growth of numbers is so massive as to impede the economic development necessary to improve living standards.

It appears then that a substantial portion of the world is caught in a vicious circle. Impoverished and agrarian, it is making strenuous efforts to improve itself. It is borrowing technology, commercialism, and capital from the West. It is also borrowing public health measures and is reducing its mortality, in some cases phenomenally. But since it is not

reducing its fertility, the result has been such a rapid growth of numbers that per capita real income has not risen much, or in some cases has been reduced, despite heroic efforts to increase the national income. Thus the present trend contains a strong element of self-defeat in it.

It follows that if the rate of population growth could be reduced by lowering birth rates in the great peasant-agricultural regions of the world, the pace of economic advance and of social modernization would undoubtedly be quickened. Individual welfare would be enhanced and the benefit to mankind as a whole would be incalculable. Indeed, hardly any other change can be imagined which would have such far-reaching effects.

It is not a question of choosing either economic development or population control to the exclusion of the other. Both are essential. Most of the controversy over the population problem seems to rest on the implicit assumption that one or the other is necessary but not both. Actually, prosperous countries are those with reasonably low fertility, but low fertility by itself cannot bring prosperity. Similarly, poor countries are generally those with high fertility, but they are not poor solely because of their birth rate. The "either-or" assumption in discussions of the population problem apparently stems in part from a false idea of causation and in part from the sheer logic of controversy itself. When confronted with a concrete condition (e.g. poverty) which is the result of interrelations between several variables, the mind tends conveniently to seize one variable and ignore the others. This deterministic tendency is strengthened by controversy, for in the heat of debate over different policies, each side strengthens its own position by choosing the particular determinism that fits its position. Thus the opponent of birth control finds it convenient to believe that economic development

can indefinitely take care of population growth, and he readily misinterprets his opponent's position to mean that economic development has nothing to do with the level of living. The rabid birth-controller, on the other hand, is likely to regard with suspicion any attempts at economic development and to leave the impression that the widespread adoption of birth control would solve all problems. In other words, "either-or" thinking goes hand in hand with the advocacy of a panacea.

Quite apart from oversimplified determinism of this character, the question is frequently raised as to whether or not anything can be done about the birth rate prior to a country's economic and social modernization. In the history of the West and in Japan, fertility has fallen only after there has occurred a great deal of urbanization and industrialization. These new conditions of life have two effects: First, by lowering the infant mortality, they cause the old fertility to yield an increased family size. Second, by making social status more fluid and competitive and more dependent on the individual's own effort than on that of his family, they cause children to become a greater burden than formerly. Among a rural peasantry, on the other hand, the same institutions and attitudes tend to persist which have for centuries produced a level of fertility high enough to overcome the normally great mortality and thus to enable the society to survive. If the death rate remains excessive, then a high birth rate is functionally adapted to the situation and there is not much population growth. But every day our ability to control disease in backward areas is becoming more manifest. Yet fertility does not decline correspondingly, because as long as the economy remains rural, the old institutions governing fertility seem appropriate. The suggestion is therefore frequently made that there is nothing

that can be done about the birth rate until a country has become urban and industrial, and that once this happens, the adjustment of fertility will take place almost automatically.

But this argument, sound as it seems in view of the history of demographic change in the last century, has one weakness. The backward areas of today are not in identically the same situation as the backward areas of yesterday. In most cases, they have long had contact with the West, usually in a colonial status, and they have built up population densities far heavier than they could have achieved without such contact. Now if we imagine that they will go through the "normal" process of urbanization and industrialization, we must recognize that their fastest population growth is still to come. Yet in many areas a future doubling or tripling of the population seems out of the question. It certainly seems incompatible with a concurrent rise in the level of living. It would mean, indeed, that all of the industrial and agricultural arts would have to be used merely to support people at a subsistence level, a level so low that, paradoxically, the advanced arts could not be sustained. Thus the related ideas of a "normal" population growth and a "normal" industrialization such as occurred in Western Europe and in Japan now seem mutually incompatible in the world as it exists today.

Further proof of this incompatibility lies in the accumulating evidence that population growth and density are making ever more difficult the achievement of economic development, especially now that mortality is being reduced rapidly in backward areas. Death rates have recently been lowered in certain underdeveloped areas faster than they were ever lowered in the past in the countries now economically advanced. In Ceylon, for example, the use of DDT for mosquito control in malarial areas brought

the death rate down from 22.0 in 1945 to 12.6 in 1949. Since fertility rose slightly during this period--due also to the control of malaria according to some statisticians in Ceylon--the resulting rate of natural increase per year has risen from 14.7 per 1,000 in 1945 to 27.3 in 1949 and 27.7 in 1950. A study of the crude death rates throughout the South Asia and Near East area shows that almost universally there has been a downward tendency, especially in years since World War II; but birth rates remain virtually fixed. Modern medicine, applied by technicians on a mass basis, is creating a new situation in backward areas. Not only in Ceylon but also in Puerto Rico, Formosa, Cyprus, and Malaya can this new situation be seen in its extreme. Rates of increase in underdeveloped countries are becoming as high as they were in industrial countries in the heyday of their industrialization; yet a comparable degree of industrialization is not occurring. It is a situation so anomalous that it seems highly unlikely that it can continue.

It thus appears imperative that an attempt be made to bring down fertility in overpopulated regions without waiting for a remote, hoped-for transformation of the entire society. If mortality can be reduced by 50 per cent in a few years without industrialization, there is no proven inherent reason why fertility too cannot be drastically reduced. Fortunately, several governments in the affected areas are interested in controlling the rate of population increase among their people, because they see at first hand the difficulties brought by rapid growth.

The task, however, is not an easy one. The lowering of fertility on a massive scale <u>prior</u> to a country's urban-industrial transition has never occurred in human history. There are instances of low fertility among primitive peoples, and some agrarian societies have lower birth rates than

other agrarian societies.* But, while these cases show that it is possible to have low fertility without urban-industrialism, it nevertheless remains true that a modern demographic balance on a massive scale has never been achieved prior to economic modernization. Such a step would therefore be revolutionary, and it can be taken for granted that a weak, half-hearted effort will not accomplish it. In fact, a concerted and large-scale attempt, using the resources of every branch of physical and social science, will undoubtedly be required.

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* The primitive cases fall into two classes: first, those who have a low mortality due to a protected environment and who therefore have worked out means of adjusting their birth rate to this low mortality; second, those who have been disorganized and ridden with venereal disease due to contact with European civilization. Among peasant societies, it is noteworthy that the fertility of Moslem peoples is almost universally higher than that of Hindu and Buddhist peoples.

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## The Question of the Means of Fertility Control

The present plan for a program of action concerns itself with only one facet of the population problem---namely, the development of new methods of fertility control through research in the biological and medical sciences. Why this facet is of peculiar importance at the present time requires discussion.

The claim has often been made that one of the difficulties standing in the way of bringing lower fertility to peasant peoples is the inappropriateness of presently-available birth control methods. The techniques that have worked reasonably well among advanced industrial peoples are not necessarily the ones that will work well among those who live close to subsistence, who enjoy little or no privacy in their homes, possess

practically no sanitary or storage conveniences, and have little education. This interpretation has been at least partially demonstrated by studies of attempts to bring fertility control to backward areas in the United States, Puerto Rico, and elsewhere. Beebe, who made by far the most thorough of these studies, has this to say concerning the experiment in Logan County, West Virginia:

> "The Logan experience fits into a general pattern characteristic of rural series of similar nature. A great increase in protection occurred because more women practiced contraception more of the time, even though their efficiency was none too high. The prescribed method (jelly alone) proved to be little, if any, more effective than methods already known to the patients...All present methods have evident shortcomings which severely curtail the usefulness of any single method. Only the development of radically new methods which would be relatively independent of the motivation and skill of the patient could overcome the present necessity for making use of a greater variety of methods in any service like that extended to the Logan patients." *

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* Gilbert W. Beebe, Contraception and Fertility in the Southern Appalachians (Baltimore: Williams and Wilkins, 1942) p. 153. See also: Beebe and J. S. Belaval, "Fertility and Contraception in Puerto Rico", Puerto Rican Journal of Public Health and Tropical Medicine.

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If peasant peoples have not taken to currently available contraceptive methods, it is not because they are inherently opposed to scientific instrumentalities or technological change. They have in most areas accepted vaccination against smallpox, inoculation against cholera, measures for mosquito control, medicine for malaria, or sanitation of water supplies. There is hardly an area so remote that it has not seen and accepted some application of medical science to health problems. It has not been so easy to influence the peasants' personal hygiene or to get them to take the initiative in behalf of their own health, but the fact remains, as

noted above, that measures introduced for their health have almost universally lowered the death rates, in some instances spectacularly. It therefore seems plausible that acceptable birth control techniques might be found, and that the application of science to developing such techniques for peasant regions might yield revolutionary results.

Unfortunately as yet, the control of reproduction has been neglected as a field of natural science. While almost miraculous achievements have been made in the treatment of ill health and the reduction of mortality, very little has been done by way of scientific research on fertility control. To be sure, much has been accomplished with respect to a better understanding of human reproduction, especially in recent years, but this branch of basic biology has not received the attention it deserves from a medical standpoint and has hardly been applied specifically to the development of new and more readily acceptable methods of birth limitation. In view of the imbalance between the birth rate and the death rate in many impoverished areas of the world, in view of the threat of future population growth to levels of living, this "blind spot" in the application of medical and biological science is an anomaly--many would say, a tragic anomaly.

It is sometimes said that where the motivation to limit births is strong, the means to do so will be found, and that therefore the important thing is to create a desire to control the number of offspring rather than to provide the means. This is only a half-truth. As Donald Marquis stated at the Williamsburg conference in June, 1952, the action of a couple in limiting or not limiting their fertility is a product of two

things, their motivation and their means.* As the one is weak, the other

* This thought has been stated slightly differently by Beebe: "....The necessary and sufficient conditions for contraceptive practice are three: motivation, knowledge of the means, and accessibility of the means. Although none is sufficient, a high degree of motivation occasionally compensates for ignorance or for poor access to materials." Op. cit., p. 125.

must be strong. If there is no motive at all, the best means conceivable will be of no avail. But if the motive is weak, the behavior will hinge on the convenience of the means.

In peasant societies today, it seems clear that the desire to limit births is weak, but it is equally clear that the desire is not absent altogether. Field studies in India, Puerto Rico and Mexico, for example, have shown the existence of a desire among village folk to have only two, three or four children. Primitive societies have frequently been observed to limit reproduction deliberately in various ways.** In fact, attitudes

** See Norman E. Himes, Medical History of Contraception (Baltimore: Williams & Wilkins, 1936), Parts 1-4; Clellan S. Ford, A Comparative Study of Human Reproduction, Yale University Publications in Anthropology, No. 32 (New Haven, 1945), pp. 41-43; Raymond Firth, We, The Tikopia (London: 1936), pp. 408-493; M. Soors, "La denatalite chez les Mongo", Zaire, Vol. 4 (May 1950), pp. 525-532.

and practices opposing unrestricted reproduction have been current in all ages. There is no society in which the level of reproduction comes anywhere near the biological capacity of the human species.***

*** Some of the restraints upon fertility are not deliberately adopted for this purpose but rather are part of the customary institutional structure. See Kingsley Davis, Human Society (New York: Macmillan, 1949), pp. 557-561.

It must be stressed again that peasant societies in the modern world do not live under conditions identical with those under which they lived previously and in which their mores and institutions yielding high fertility were evolved. People in all regions have been affected by commercial and political contact with the West. The very reduction of mortality in most parts of the world has led to an alteration of conditions. It has meant, as already mentioned, that the same fertility yields larger families than formerly. Since most of the reduction in mortality has been made in the infant and childhood ages, the peasant now finds that, without any change in his reproductive practices, he has many more children to provide for than his ancestors had. In addition, the resulting population growth has altered the economic situation for the peasant. Agricultural land has become scarce and high-priced. The woodland and pasture once available to the village has been used up or put to the plow, and erosion has taken its toll. Finally, the increasing familiarity with manufactured products, with a money economy, and with commercial agriculture, has brought a desire for an enhanced standard of living. Although often painted as a docile automaton anxious to have only enough to eat from food that he grows himself, the truth is that the peasant in the modern world is a revolutionary man. He is the man who is changing his entire mode of life in China and Korea, who supports agrarian reform throughout Southeast Asia, who creates, with his desires and complaints, political concern and disturbance almost everywhere. To assume that this man has no thoughts and no desires with reference to the size of his family or the future of his children is surely an error.

If, then, there is a desire to limit fertility, but not a strong

enough desire as yet to override all limitations of means, an obvious path to pursue is to improve and make more available the means of family limitation. To be sure, the provision of such means cannot be viewed as a panacea or an alternative to other measures. The motivation to control fertility requires strengthening. Educational work will be necessary in order to improve the peasant's understanding of the implications of large and small families. Legal and economic measures will have to be undertaken to give him a sense of responsibility and a concern for the future of his children. Any work on the means of family limitation is therefore only one facet of the total attack on the population problem in densely settled agricultural areas.

Although such work would not help much if pursued alone, the improvement of the means of fertility control is nevertheless an important and neglected facet. The discovery of systemic, or physiologic, methods readily applicable under peasant conditions, divorced from the sexual act itself, lasting over an extended period, and requiring a minimum of expenditure, inconvenience and education, would enormously increase the likelihood of fertility control in the regions where it is urgently needed. This would mean that the strides made in world health would be matched by corresponding strides in rational reproduction, to the benefit of world living standards. It would mean that the current anomaly of rapid population growth in economically stagnant areas would be eliminated and the danger of catastrophic rises in mortality would be reduced. At the present time, there is hardly a more crucial aspect of the population problem.

## Chapter II

## THE TARGET: GOALS AND MEANS

It should be clear from the preceding section that the ultimate goal with which we are concerned is a solution of the world's population problem. This problem, more acute today than it ever has been in the past, is capable of being solved. In fact it has been solved satisfactorily in certain countries, so that we know that a solution in the rest of the world is at least possible.

Once the goal is realized clearly, the interest then shifts to the problem of means. So far the major means pursued has been that of economic development. But such a means, although unquestionably necessary and beneficial, is futile if pursued by itself. Equally necessary is the control of population growth, and we have therefore tried to balance the books by confining our attention to this particular aspect of the problem. Specifically, we have visualized the central means, for our purpose, as being the rather rapid reduction of fertility in the underdeveloped but crowded areas of the world. The achievement of this task would remove the pressure of population as a depressant of the world's standard of living. It would enable economic development to take place more rapidly, would reduce some of the international strains growing out of the imbalance of population growth as between nations. In short, the accomplishment of this undertaking, along with economic advance, would surely solve the earth's population problem.

But how to bring down fertility in underdeveloped areas? Here the problem of means divides itself into two parts. On the one hand, as we have seen, there is the question of motives, and on the other there is

the question of instrumentalities. On the motivational side, if fertility is to be reduced, the peoples concerned must somehow come to appreciate the desirability of having a reasonable number of offspring--reasonable in terms of the care and education they can give them, reasonable in terms of the number necessary to replace the older generation, reasonable in terms of the adequate spacing of births. The character of parental motivation seemingly depends on social-economic conditions, for these determine the interests that people have in children. This is why, in the history of the urban-industrial nations, the birth rate eventually declined; the changed conditions forced parents in their private capacity to limit their fertility. In the preindustrial regions of the world today, as we have seen, conditions are changing, but they are not changing in precisely the same way as the industrial societies changed in the past. Any full-fledged program of dealing with the population problem must therefore give attention to influencing motives and attitudes. A way must be found to bring the popular notions of childbearing into adjustment with the changed conditions, and at the same time the conditions themselves must be further changed through economic improvement and social modernization. Every attempt must be made to raise the standard of living, particularly in those ways that will yield a greater reward for planned than for unplanned fertility.

Our particular work, however, is not an attempt to solve the population problem in all its aspects. It is rather an attempt to solve only one aspect of the problem, an aspect which has so far been neglected. We are trying to work out a sound program of scientific development which will ultimately provide better instrumentalities for fertility control in underdeveloped areas. We are trying in this way to provide a means of

compensating for weak motivation. Undoubtedly the question of motivation will have to be tackled at later stages in the program, because a necessary element in the feasibility of any particular method of fertility control is its popular acceptability. In other words, a physiologically adequate means is not necessarily a satisfactory means. For this reason the program of applying physiological science to the problem of fertility control eventually must be joined to a program of testing the most promising leads in actual community situations. At this point the approach of the natural scientist must be joined with that of the social scientist.

Schematically put, then, our immediate targets are as follows:

I. To foster scientific development in the field of fertility control.

II. To reach through this development a radical improvement in the means of fertility control for underdeveloped areas.

III. To reach also new methods of aiding otherwise childless couples to have children.

IV. To test in various cultures the acceptability and adequacy of the most promising methods developed.

Each of these merits particular discussion.

## Scientific Development

Our deliberations have been primarily for the purpose of determining whether or not the field of fertility control is yet ready for a concerted program of scientific application. Attention has of course been given to the question of whether or not there is a need for such a program, and this has been answered in the affirmative. This granted, the next question was whether or not the basic science has yet reached a stage where detailed and productive research applied to fertility control can be

envisioned. This question too has been answered in the affirmative. The reasons are given more fully in a later section where the scientific possibilities are discussed in detail. At this point all that need be said is that there are gaps in our basic knowledge of human reproduction, that these gaps are currently being gradually overcome, and that in the case of some possible avenues to fertility control more basic research is needed. But at the same time the state of underlying knowledge in this field seems already sufficiently advanced to justify fully a planned program of further scientific development. Such a program would inevitably encourage at certain points the pursuit of highly selected research in basic science. Much of it, however, would be devoted to applied research--i.e., research where the steps necessary to develop and test a possible application can be seen in advance. Such applied research would certainly contribute in turn to basic science, but it should be clear that the program envisioned will be focused primarily on applications to fertility control rather than on general basic research as such.

## The Type of Controlling Agent Desired

Among the outcomes of the program envisioned would be certain new means of controlling fertility. In order that these new means be successful in maximizing the effectiveness of the nascent desire for family limitation in high fertility regions (however weak the desire may be), they should, ideally speaking, meet very nearly the following stipulations:

1. Convenience for the individual. The method should not require that the users store anything, go to much trouble to get the materials, or take many pains in the use of the method.

2. Simplicity in use. It should not require any education or training to use, nor should it require much time on the part of a third party, such as a doctor or a social worker.

3. Divorcement from the sex act. The means with which we are generally familiar, except sterilization and abortion, are used in connection with the sex act specifically. They thus require a rather unhappy combination of reason and passion at the same time. This fact is especially a hardship in cultures (such as India) which rigidly segregate the roles of men and women and ban communication about sex matters between husband and wife.

4. Persistence through time. In order to divorce fertility from the sex act and to achieve maximum convenience at low cost, the means of fertility control should be such as to endure over a considerable period. A method which, applied once, will last for months or even years, would be highly desirable for peasant populations.

5. Cheapness to manufacture and deliver. For people with incomes little above subsistence, the necessity for a low-cost contraceptive has been justly emphasized. This feature has, however, been stressed on the assumption that the cost would be met by the individual out of his own pocket. It is essential to recognize that in certain countries the government may be willing to meet the cost, the individual user not being charged at all. Of course, even in this case, the cost would have to be low, but the very fact of government purchasing in bulk would tend to lower the unit costs and would release the individual from any feeling of competition between birth control and other demands on his limited funds.

6. Convenience in handling before it reaches the individual. Since the system for distributing goods is inefficient and time-consuming in peasant-agricultural communities, a usable means for controlling births should not require much special handling, such as refrigeration, reprocessing, mixing, measuring, or selling, or suffer from rapid deterioration.

7. Freedom from deleterious effects. It goes without saying that the use of any widely acceptable method should be accompanied by no harmful side effects. Certain mechanical contraceptives of the past, such as the stem pessary, have been defective on this score.

8. Reversibility of the means. It also goes without saying that any method of birth limitation, to achieve maximum acceptance, should be reversible. The couple should be able to omit it when offspring are desired.

9. Absence of any effect on the sex urge. Among the deleterious side effects to be avoided is any lessening of the sex urge. In virtually every society masculine potency has an extremely high value, and any fertility control measure which impaired it would certainly fail of acceptance. The same importance cannot be attached to possible effects on the female, since sexual enjoyment on her part is deprecated in many societies. Yet, from a humane point of view, the desirability of not lessening sexual pleasure or reproductive capacity in either sex seems clear.

Necessarily, no invention is likely to fulfill perfectly every one of these requirements, yet the necessity clearly exists for fulfilling them as nearly as possible. The birth control methods of urban-industrial populations fail to meet certain of the requirements altogether, though they meet others rather well. The rationale for scientific research in this field is the possibility that the technology of fertility control can be greatly perfected, bringing us much nearer to the kind of method ideally envisaged. Presumably this technological improvement can best be accomplished through the application to this problem of the sciences dealing with reproduction in all its biological and medical aspects.

## Should Attention be Given to Sterility?

It has not been possible to get agreement in the working group on the question of whether or not the program should include work on the means of treating and preventing sterility. Those holding the affirmative view say that giving attention to sterility would gain good will for the program, would advance our basic knowledge of reproduction, and would give a positive slant to an otherwise "negative" program. It is pointed out that in every country there are a good percentage of couples who cannot have offspring. Nowhere is the desire to limit offspring really a desire to have no children at all; sterility is therefore almost universally regarded as a calamity. In the United States in particular the

interest of the public in overcoming sterility is substantial. In view of these considerations, some members of the working group have thought it would be wise and humane to include in the fertility control program a minor degree of concern with problems of sterility.

On the other hand, others of our members have pointed out that funds, facilities, and scientific attention are already being devoted to sterility and will continue to be so devoted. It therefore seems unfair to divert any effort from the fertility-control problem (which has been starved for support and scientific attention) when our program is specifically designed to help balance the picture that has prevailed in the past by giving major attention to the scientific aspects of fertility control.

In the absence of agreement in the group, this question can be left to those who will direct the program to decide.

## Field Testing

Involved in a program of scientific research on new methods of fertility control will necessarily be both laboratory and clinical testing of products. However, there will come a point when such products as pass these initial tests will be tried out on a community basis. There are some methods of birth control that are already available for such community testing. One, for example, would be the newer techniques of vasectomy.

Field testing on a community-wide basis is really concerned with the problem of acceptability and with the educational techniques necessary to foster public cooperation. It involves an understanding of research methods in public opinion analysis, the study of mass media communication, and demographic and survey statistics. It therefore calls for social scientists well-versed in designing experiments in which such skills are important.

Furthermore, community testing exposes the investigators to more possible reactions from pressure groups than does any other part of the program envisioned. The rest of the program, so far as the general public is concerned, comes under the heading of strictly scientific research. Community research, on the other hand, is generally confused in the public mind with outright propaganda and advocacy of a cause.

Both because of the special techniques required in community studies and because of the exposed position of the investigator, it is probably desirable to keep the community testing program separate from the program of scientific research. In this way, issues growing out of the community work will not run the chance of interfering with the other phases of research. Community testing is included here as one of the goals because it is integrally connected with the whole program. But in the discussion of organization below, the question will be raised as to whether or not it may prove more feasible to get this testing done under a separate aegis. Undoubtedly, there should be close liaison between those responsible for the research in the natural sciences and those responsible for the community studies, and this can doubtless be worked out on an informal basis. It is questionable, on the other hand, whether any formal organizational structure linking the two should be adopted.

## Conclusion

We have now discussed what seem to be the major goals of our program. These, it is hoped, will become clearer in later sections, and the reasons will become evident as to why these are the goals. The logic of our position will be seen especially in the next section which deals with the scientific leads that our conferences with scientists in various fields have disclosed in some detail.

## Chapter III

## THE POSSIBILITY OF ACCELERATING SCIENTIFIC DEVELOPMENT IN METHODS OF FERTILITY CONTROL

If the desirability of finding new methods of fertility control be granted, the next question is this: Would a planned program of applied scientific investigation speed up the discovery of such new methods? Since science normally makes progress anyway, would it not be better simply to support basic biological research and wait for inevitable applications to fertility control to be made?

The answer is two-fold. First, as already mentioned, for reasons that are well-known, this aspect of science has long been neglected and is likely to continue to be neglected if nothing is done about it. There is a great amount of investigation under way in the physiology and biochemistry of reproduction, though not so much as there might be. There is a considerable interest in sterility. But the social barriers to scientific research on measures of fertility control are great, and unless something is done by way of a planned and concerted program to counteract them, there will continue to be a lack of incentive on the part of reputable scientists to enter this field. For this reason it would seem that an attempt to speed up scientific discovery is peculiarly appropriate. We believe that there are ways of overcoming the factors that in the past have kept scientists away from fertility control as a legitimate field of applied science. These ways are discussed at length in Chapter V on the organization and nature of the proposed program.

Second, our basic knowledge has reached the point where a fruitful applied program can be visualized. Twenty-five years ago there would have been far less reason to talk about a program looking toward physiological means of fertility control. No one knew enough to say clearly

where one would start in such research. The funds would have had to be expended simply in basic research in the general field of mammalian fertility. It would have been difficult to speed up this basic research, because such work is an organic process that cannot be forced by pouring large sums of money into it.

However, because such basic research was done in the last twenty-five years, enough is now known about the physiology of reproduction to say that a fruitful program of applied research can be mapped out. The stage has at last been reached when one can explicitly state the experimental steps that have to be taken in order to decide in favor of or against any one of a number of specific methods for reducing fertility. One can determine what animal experiments should be run, what clinical tests on human beings should be made, etc. It is therefore indeed possible to accelerate progress by making funds available and by sceing to it that these funds are wisely allocated.

This conclusion concerning the readiness of the field for a planned program of applied research has not been reached suddenly or dogmatically. It was in fact the question that occupied a group of highly qualified scientists for several months. In the next chapter the major grounds for accepting the conclusion are set forth. For the moment, to acquaint the reader with the necessary background for interpreting the findings, we give the history of how this group was formed and how it worked.

In the spring of 1952 The Conservation Foundation, as part of its exploratory work in the field of population, decided that it would be of some importance to look into the possibility of finding new methods of fertility control more suited to peasant populations than those methods now in existence. Using some of the research funds it had allotted to

population, the Foundation elected to have a rapid survey made to see if the matter would be worth pursuing further. Since much of the necessary knowledge is recent and since much of it has been done for purposes other than fertility control and is therefore difficult to find in published form, it was decided that the best method of accomplishing this would be to concentrate on interviewing the outstanding authorities in the relevant scientific fields, particularly those people who were known to have an interest in applications to fertility control. Dr. Paul S. Henshaw, who had long been with the United States Public Health Service, was then employed to conduct the survey in cooperation with Kingsley Davis who was in charge of the Foundation's work in population.

For seven weeks, beginning April 1, 1952, Dr. Henshaw traveled to major medical, research, and university centers in the country. He interviewed over seventy-five authorities and delved as far as possible into the research literature, attempting to put together a reasonably complete picture of those major developments in the physiology and biochemistry of reproduction which appeared to give promise of ultimate application to fertility control. At the end of the period, with the help of two expert consultants, he prepared a report of some fifty-six pages embodying his findings.

This report, though quickly prepared and necessarily tentative and incomplete, was nevertheless sufficiently sound and optimistic to convince the officers of The Conservation Foundation that a long-range program of applied scientific research would perhaps be feasible at this time. Since the Foundation felt that the goal of such a program would, if achieved, be of the utmost importance to human welfare (at least potentially), it was decided to go into the matter more thoroughly. This decision was

strengthened by the Conference on Population Problems convened at Williamsburg, Virginia, on June 20-22, 1952, under the auspices of the National Academy of Sciences and of Mr. John D. Rockefeller III. A considerable body of opinion at this conference felt that one of the clearest ways in which a solution of the world's population problem might be fostered would be through the development of new methods of fertility control meeting some or all of the criteria set forth above as the "target". Although opinion was not unanimous that basic science had in fact reached the point of justifying such an applied program, it was seemingly in greater agreement on this question than on any other discussed. The one qualified person who had the greatest reservations, Dr. George W. Corner, later became much more friendly to the idea when the findings of the Henshaw survey and the possible modes of procedure in a long-range program were explained to him in detail.

Feeling strongly that the matter merited a more thorough exploration, The Conservation Foundation found itself asking how this exploration could best be pursued. At this point Dr. Leo Szilard of the University of Chicago came upon the scene. It soon appeared that he had been thinking strongly that a very thorough investigation of the possibilities of new fertility control measures should be made, and that attempts should be made to plan tentative organization for a program of scientific research. He had some definite ideas as to how this investigation and planning should be done.

As a result of numerous discussions, it was decided to undertake such an investigation. The purpose would be to reach a firm conclusion on whether or not the stage at present reached in science warrants a planned program of applied research in fertility control, to assess the

various kinds of research leads that would possibly be pursued in such a program, and to plan at least tentatively the organization, budget, and personnel of the program. This task, it was agreed, should be accomplished by getting a small working group together which would bring in expert witnesses to discuss frankly and at great length the various aspects of the problem. The procedure would thus be something like that of a Royal Commission. The working group would consist of both laymen and experts in the field in question, and the witnesses would be called by virtue of the special knowledge they possessed.* An attempt would be made to record the proceedings and thus to have a permanent record of what transpired.** As a result of these sessions, a full report would be prepared by members of the working group, this report to be of service in any subsequent steps that might be taken.

This plan was put into operation in early September, 1952, in the offices of The Conservation Foundation. Shortly after the work had begun, on September 12-14, the Planned Parenthood Federation of America, under the name of its research arm, the Robert L. Dickinson Memorial, called a conference at Arden House "to consider the value of leads for physiologic control of fertility" and to make recommendations concerning the future lines of development. The members of the working group were invited to this conference and derived considerable help from the discussions that took place.

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* A list of the members of the working group and of those consulted will be found in Appendix I.

** The proceedings of these conferences are contained in Appendix II of the present report. They are not verbatim but rather represent summaries and they are to be treated as strictly confidential.

During the course of its sessions, the working group was impressed by the interest and ready cooperation of the scientists it asked to appear before it. Dr. Henshaw had earlier been struck by the sympathetic interest of the men he had interviewed, and the serious concern shown for the subject was also evident at the Arden House Conference. There was, and is, a general feeling that much is happening in the sciences dealing with human reproduction and that the application of the new knowledge to population problems is a matter of the gravest importance.

The working group concluded its sessions by the end of September. It did not do so because it felt that it had exhausted the subject. Indeed, the discussions led in far more directions than had originally been anticipated. But it was felt that enough had been learned to answer with some assurance the main question at issue. The present report attempts to present in brief compass the main findings and conclusions which came out of the survey, together with recommendations based on them. It attempts to show why a program of applied scientific research in the field of fertility control is both feasible and desirable at the present time, to suggest the possible scope and organization of such a program, the approximate cost, and the conditions of success.

## Chapter IV

## CONTROL OF PHYSIOLOGICAL FACTORS IN FERTILITY

The basis for anticipating the eventual control of fertility by physiological means can be stated quite briefly. The reproductive process is a delicate chain of events depending upon an intricate biochemical system of checks and balances, of events geared together in terms of critical substances, critical amounts of these substances, and critical timing. Numerous links in this complex chain are subject to interruption or modification in one way or another. Many interruptions are known to occur without deliberate intention as abnormalities or accidents of one sort or another. In the female, however, regular intervals of infecundity occur as part of the normal cycle and can in no sense be described as abnormal. It appears possible--indeed, it has already been established in principle and in fact--that the process of reproduction can be halted at one or more points by relatively small changes, some of which may persist over time in their effects without harmful effect upon the maternal organism.

Whereas the traditional methods of birth control, with the exception of the "safe period," are either mechanical or spermicidal in character, the new possibilities of which we are speaking lie mainly in the direction of affecting the physiology of the organism. This basis, therefore, rests upon a deeper knowledge of human physiology than do the traditional methods. This is why they are characterized as physiological approaches to fertility control.

By now the various methods of physiological control which have been mentioned, proposed, or tried on either lower mammals or human beings, have become quite numerous--certainly more than fifty. Even if those which seem patently far-fetched are ruled out, we still have a substantial number of leads which it would be feasible to explore further by way of research. In general, the thirty-odd physiological approaches that have been seriously suggested at one time or another can be classified into groups according to the step of the reproductive process which they are designed to interrupt or influence. The critical points involved in these approaches are: (1) suppression of the sex cycle in the female; (2) suppression of ovulation; (3) prevention of spermatogenesis; (4) prevention of spermatozoa survival or migration in the female genital tract; (5) prevention of fertilization of the ovum; (6) interference with the process of implantation of the blastocyst; or (7) prevention of further development of the recently implanted ovum. Some of these approaches have been successfully employed in animals under conditions of experimental observation. A very limited amount of clinical experience of a similar nature is also available. Most of these methods involve the use of a substance that can be taken orally, but a few require administration by injection. No one appears as yet to have endeavored to combine and evaluate the effects of two or more of these methods in a single course of treatment.

## Types of Specific Research Leads

Twenty-five approaches to physiologic fertility control, all of which were discussed in the meetings of the working group at the Conservation Foundation, are described in the Appendix. In the present chapter a few of

them are described briefly, solely to illustrate the range and character of the approaches. Choice of any one of them for discussion is not meant to imply that it, or some modification of it, is the best lead currently available. Nor is the order in which they are presented meant to convey any impression of priority. All are considered promising for further investigation by some authorities, as are the other leads not presented here, but described in the Appendix. Moreover, there is no doubt that new research, at present undreamed of in the realm of basic mechanisms of the sex and reproductive cycles, will add substantially to the methods that are now ready for programmatic investigation.

In both this chapter and the longer Appendix, the details given are brief. It is difficult, therefore, to introduce all the qualifications that ought to be presented. A thorough scientific account of the present status of our knowledge on each lead would make necessary a different and more extended manner of presentation. The reader is therefore reminded that what is given here is, in the eyes of the working group, no substitute for a technical coverage of the material in the field. Our purpose is not a detailed treatment but rather a sound appraisal of the potentialities for research in this field along a number of promising lines. Needless to say, the listing of a lead for research implies no advocacy of it in practice. Our purpose is purely to suggest some of the scientific possibilities.

The examples of research leads cited below are grouped, insofar as knowledge of them permits, according to the main points at which they presumably affect the physiological mechanism of the sex and reproductive cycles. Such a classification should not be construed as implying greater knowledge of the entire field than now possessed, but should be taken simply as a convenience for the reader.

## Suppression of the Sex Cycle

Extracts from the root, flower and seed of *lithospermum ruderale*,

allegedly used by the Shoshone Indians to reduce fertility, have been shown to suppress the estrous cycle of mice for long periods without causing any permanent, irreversible damage. The animals become pregnant soon after treatment is discontinued. In England, this agent is now being tested in women on a very small scale. This substance, or one resembling it, may conceivably prove to be acceptable for suppressing the cycle without any unacceptable side effects.

It should be mentioned that the physiological mechanism of the drug's action has yet to be determined.

This particular lead is a clear case of something that is ready for program research. Apart from establishing the physiological mechanism of the action of this drug and also identifying the active chemical agent contained in it, there is need both for considerable animal experimentation and clinical research. It would be desirable to conduct experiments on primates with standardized extracts of the plant in order to determine possible undesirable side effects. Arrangements could be made for clinical research, preferably in areas where other methods of birth control are infrequently practiced but where clinical facilities are available to permit observation of undesirable side effects of the drug.

## Suppression of Ovulation By Steroid Hormonal Compounds

A class of compounds, called steroids, plays an important role in the physiology of reproduction. Testosterone, the male sex hormone, falls into this class and so do the naturally-occurring estrogenic hormones of the female. Progesterone, a hormone secreted by the corpus luteum, affects the

endometrium of the uterus, making the latter capable of receiving the ovum. It is also a steroid. Some of these steroids if administered in sufficient quantity will suppress ovulation as long as their administration is continued. One may think therefore of the possibility of administering such steroids for the purpose of controlling fertility. The medication would have to be maintained as long as the avoidance of pregnancy was desired. It is generally believed that when medication is stopped, ovulation will start again so that there is no necessary danger of causing irreversible sterility. However, there is a great deal to be learned about the application of these substances to fertility control. The minimum effective doses required for inhibiting ovulation need to be established; the best substance for the purpose needs also to be ascertained.

Progesterone will also suppress ovulation if given in amounts of 250 mg. per day (injected). The minimum effective dose is not known. While it does not produce any of the side effects which are common to the estrogens, it leads to bleeding from the uterus (withdrawal bleeding) when administration is suddenly stopped. The minimum effective dose for suppressing ovulation without this untoward side effect has not yet been determined.

Progesterone itself is one of the cheapest steroid compounds, costing today 50 cents per gram if purchased in large quantities. If a dose of 25 mg. per day should prove to be sufficient, the total cost would amount to about $5 per year per woman under treatment. Whether or not this cost is tolerable will have to be investigated. With greater production, the cost per gram might be much less.

By Non-hormonal Substances

There are a number of low-cost synthetic drugs with estrogenic activity, e.g. stilbestrol, hexestrol, vallestril and others. At least one of them,

stilbestrol, will suppress ovulation as long as it is given in large quantities, but the minimal effective dosage is unknown and research is necessary to afford knowledge of the minimum effective dosage for suppression of ovulation in relation to other estrogenic effects. These compounds when given in large doses will not only suppress ovulation but also menstruation. This would make the method unacceptable for many regions unless a dosage could be established at which ovulation remains suppressed but menstruation is not appreciably disturbed.

Animal experiments seem to indicate that some of the weaker-acting estrogens, which are not hormonal substances, will suppress ovulation only if used in such large amounts that their estrogenic effects become pronounced. It is conceivable however that some estrogenic compounds within this class might be finally found that will suppress ovulation in a dosage at which the other estrogenic effects are negligible.

It appears rather likely that some compounds derived from progesterone might suppress ovulation (presumably by suppressing some of the gonadotropic hormone secretions of the pituitary gland) without having any progestational effect on the uterus. It is possible that administration of such compounds might not lead to withdrawal bleeding, in which case they might be preferable to progesterone.

Before proceeding to field tests of the above methods, it will be necessary to do further animal experiments and to arrange for small-scale clinical testing. One would, for instance, want to determine the dosage at which a number of compounds related to progesterone will suppress ovulation in the rat and other animals. Moreover, clinical tests will be necessary to determine the most effective and practicable routes of administration.

## Suppression of Spermatogenesis

### By Hormones

In spite of conflicting reports, the weight of evidence seems to indicate that a steady administration of testosterone will suppress spermatogenesis. Testosterone presumably affects the pituitary gland and suppresses the secretion of one or more of the gonadotropic hormones. The suppression of spermatogenesis by this method is reversible; for when administration is stopped, sperm production apparently returns with undiminished vigor.

The side effects which may be encountered with steady administration need to be determined. One such undesirable side effect which is conceivable and which must of course be guarded against is possible hypertrophy of the prostate. Another side effect might be an increase in libido without a corresponding increase in potency. Finally, it must be recognized that any method of controlling fertility by producing male sterility suffers from what may be called a demographic disadvantage in countries with high rates of promiscuity. In such areas, the treatment of only a portion of the males would not reduce fertility substantially. Only in cultures with a high degree of marital fidelity would the reduction in fertility be roughly proportional to the number of males treated.

Since so little is yet known about this method of controlling fertility, research is clearly required to reach a dependable evaluation. One should find out, for example, beyond a reasonable doubt, whether testosterone in a given dose will in fact eliminate spermatogenesis for as long a period of time as may be desired, and whether or not there is complete recovery when administration is stopped after several years of therapy. Clinical tests of this sort may be conducted in the United States with volunteers who have had

several children and who do not want another child. Further, an inquiry should be made as to whether testosterone could not be replaced by cheaper chemical analogues in the same way in which natural estrogens can be replaced by stilbestrol. The first question to be considered in this connection is that of establishing how much effective research has already gone into an attempt to find a cheap substitute for testosterone.

If manufactured synthetically in large quantities, testosterone might become available within two years at a price of perhaps 50 cents per gram. Assuming that 25 mg. per day had to be used (in an effective mode of administration), treatment would cost about $5 per year per male.

By Immunization

Laboratory experiments have shown that male guinea pigs immunized by a single injection with guinea pig sperm cease to produce viable sperm for an extended period. Since only the tubules appear to be affected, testicular hormone production should remain unimpaired and no other organs seem to be damaged. Whether a dosage can be found at which spermatogenesis will be re-established within a limited period of time after medication is stopped remains to be seen.

With reference to the question of whether this treatment would lead to permanent or to temporary sterilization of the human male, the odds for permanent sterilization appear to be rather good if we may extrapolate from the guinea pig to man. Such extrapolation, however, is highly tenuous, because the guinea pig tends to be in a class of its own when it comes to immune reactions. Moreover, immunological reactions may vary so greatly among individuals that it may prove impossible in man to determine the dosage which will cause temporary rather than permanent sterility.

## Affecting Sperm Survival and Transport By Means of Vaginal Bacterial Flora

An interesting lead, the possibilities of which are at present difficult to appraise, rests on the possibility of modifying the bacterial flora of the vagina. It is known that certain sterile women carry non-pathogenic micro-organisms in their genital tracts. They become fertile when those micro-organisms are eliminated by proved therapeutic procedures. The possibility arises, therefore, that inoculation of the genital tract with the proper kind of micro-organism might cause sterility over a substantial period of time. However, it may prove very difficult to maintain the flora in the vaginas of normal women and the same micro-organisms may have different effects on fertility in different women. Women with infected, purulent cervices frequently become pregnant with ease. Obviously, research is required to determine whether this lead should be pursued intensively. A small amount of experimentation is going forward on this lead. Much more needs to be done. Already, one micro-organism has been cultured in test-tubes, transplanted to a woman, and under highly specialized conditions involving the use of a specific antibiotic agent, transmitted to the vaginas of Rhesus monkeys where the organism flourishes for a time. The possibility exists that non-pathogenic organisms might be taken from sterile patients or cultures and transmitted to normal women in order to produce temporary sterility. It is possible too that other micro-organisms not so far identified in the human vagina may neutralize the effect of spermatozoa *in vitro* and in monkeys and human subjects.

## Affecting Fertilization

There is not, at this time, any method known for certain which will

attack the reproductive process at the point of the fertilization process. There are, in the literature, and even in the lay press, reports which claim this action. A conservative view is that the fertilization process may be affected by one of several procedures--and if the effect of a procedure is one which harmlessly affords reduction of fertility without certainty of the point of attack, it is a worthwhile lead requiring (a) basic research into the manner of its effectiveness, and (b) applied research into the value of the procedure as a fertility control agent.

With the reservations implicit in the above remarks, the following research leads may be mentioned as of interest.

By Phosphorylated Hesperidin

According to a report in Science by Martin and Beiler, administration of phosphorylated hesperidin to female rats reduces their fertility from the 80 per cent for the untreated group to 20 per cent for the treated group. This finding is promising inasmuch as phosphorylated hesperidin is a tasteless, non-toxic substance and one that could be produced cheaply from lemon and orange peel. Pursuing this lead, Dr. Benjamin Sieve, in Boston, administered this drug orally to married couples. A daily dose of 300-400 mg. was given to both husband and wife. This was a much weaker dosage, when calculated on the basis of body weight, than Martin and Beiler used in their rat experiment. Dr. Sieve reported his work recently in Science. In that article he claimed that he was able to prevent conception in the couples treated. All his patients had had children before, and of those whose treatment was stopped, practically all became pregnant again. In toto, he had about 130 pregnancies after treatment was discontinued. According to his report, in all cases the women became pregnant within three months after stoppage of treatment. This is a remarkably short period of time because even with young couples who are

at the peak of their fertility, one would expect a much higher scatter. Dr. Sieve reported a number of patients who were under treatment for fairly long periods (longer than eight months) without becoming pregnant. This would be stronger evidence of the effectiveness of the treatment if his data had shown that the treated women were not lactating during treatment. Since many women do not ovulate during lactation, and since all of his patients had given birth prior to treatment, it would be necessary to have data on the interval since the last birth and on the period of lactation. Presumably this doubt might be dispelled by Dr. Sieve on the basis of his records, but there still remains the question of whether or not his patients used other contraceptives while under treatment with phosphorylated hesperidin.

Under the circumstances it is not possible to express an opinion on the effectiveness of this drug for fertility control. This is a method for which claims have been made and it should, therefore, be thoroughly investigated in competently designed experiments. Dr. Sieve's observations are, however, encouraging insofar as absence of toxicity of phosphorylated hesperidin is concerned.

The following steps in program research seem to be indicated. First, further tests of phosphorylated hesperidin in rats and other animals should be carried out. Second, assuming that the animal experiments continued to be encouraging, carefully controlled clinical tests would be in order. These might well be conducted in regions where it is certain that the great majority of patients will not be using other contraceptives. To secure cooperation in such an area, one might select three hundred couples within the range of a clinic. These could be paid a small sum of money each for coming to the clinic daily and taking the drug in the presence of an officer of the clinic for a period of, say, a year. Every attempt should be made to detect and

measure any toxic effects that may occur. If such an experiment were carried out in a population of normally high fertility, it should show within a year whether the drug is effective in limiting fertility. Third, if the clinical test should show the drug to be efficacious, attention would have to be given to the chemical process of producing phosphorylated hesperidin. It should be improved to the point where it becomes reproducible. The drug has been made in experimental batches by the National Drug Company in Philadelphia. Dr. Martin, Research Director, informs us that the individual batches differed greatly in their physiological activity so that it was necessary to test each batch on experimental animals.*

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* The test used is based on the influence of the drug on the spreading of injected dyes in the skin of rabbits through a supposed effect on the ground substance of the tissue.

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In short, it appears that in the case of this lead, program research is not only feasible but is urgently needed. Reports in the press will undoubtedly lead to the use of the drug. Careful experimentation is needed quickly to avoid possible dangerous effects and to achieve a proper understanding of it. The promise of the drug, because of its low cost, lack of taste and apparent lack of toxicity, is very great if it proves to be effective.

By Immunization

Laboratory experiments carried out long ago suggested that the female could be immunized against male sperm. These experiments were done before the use of adjuvants in immunological work had been established. Today, it appears conceivable that if the female were immunized with sperm using, say,

paraffin oil and myco-bacteria as adjuvants, the circulating antibodies might perhaps be secreted into the genital tract and interfere there with physiological conditions essential for fertilization or survival of the egg. Even though this is a remote possibility, it should be pursued because, if efficacious, it would provide an attractive method of fertility control. A single injection might provide the immunity required and booster doses given at intervals of a year or two might prolong the immunity as long as desired.

The principle of immunization of the female affords sufficient promise to justify experimental investigation. First it would be determined whether in fact female immunity to sperm can be induced, with a resulting stoppage or reduction of fertility. Such experimentation could be carried out on whatever laboratory animals were most convenient for observation. If the results turned out to be positive, the next questions to answer would be whether or not any tissue damage occurs in the animals due to cross-immunity. In case no damage could be found, the next step would be to extend the experiments to monkeys. Finally, if the findings turned out to be similar to those established for infra-primate animals, clinical tests could be made with human beings.

## Interfering with Blastocyst Transport

The fertilized ovum, experiencing initial cell division, requires some four days to traverse the Fallopian tubes. At this time it depends upon essential secretions of the tubes, and it must reach a uterus ready to receive it within a given number of days. Interference with either of these processes may stop development of the fertilized ovum before the embryonic disc, the formative organism, becomes differentiated.

There is presented in the Appendix a consideration of the experimental procedures using estrogenic substances which (a) cause the dividing blastocyst to wither, and (b) by excessive muscular activity lock the ovum in the tube and delay its arrival at the uterus in time to be implanted.

Interfering with Endometrial Development

When the blastocyst reaches the uterus, it does not yet contain the embryonic disc, which is the formative organism. For this to develop and for implantation to occur, certain little understood biochemical substances must be elaborated by the endometrium, the tissue lining the uterus. It is clearly established, however, that certain empirical procedures can prevent the development of the endometrium which is essential for the sustenance of the ovum. In the investigation of this lead, advantage could be taken of the fact that women who have been scheduled for hysterectomies are excellent test subjects for endometrial response. We are informed that major metropolitan hospitals would cooperate fully in such work. Indeed, this is one instance in which experimentation in human subjects would be better for the purpose and cheaper than experimentation with monkeys.

By Preventing Progestational Proliferation

Experiments are described in the Appendix which show that in laboratory animals the glandular development of the endometrium can be prevented by use of estrogens. No minimal effective dose for this effect in the primate uterus has ever been determined. Moreover, analogues of estrogens or other substances having such an effect on endometrial development have not been described. Basic research might reveal other such substances.

By Preventing the Implantation Process

It is possible that pregnancy may be affected by means of a drug that will prevent implantation of the ovum. Experiments which point in the latter direction have been conducted so far only in rats and rabbits and other laboratory animals. The normal uterus responds to certain stimuli by the formation of decidual tissue which is the initial part of the maternal placenta. The experiments of Hisaw showed that this decidual development does not take place in rats to which a crude mixture containing pregnandiol and related compounds is administered. If a similar effect could be achieved in man, we might then have a very promising approach to our problem, inasmuch as we may be able to reduce fertility without producing a general systemic effect.

Work along this line ought to be pushed vigorously, because it is conceivable that a compound may be found which is effective and which has, apart from the effect on the endometrium of the uterus, no appreciable general physiological effect. Such a drug would appear a priori to be more desirable than drugs which suppress the gonadotropic hormone secretions of the pituitary, as mentioned above.

A research program could be readily set up at the present time for testing steroids in laboratory animals, including monkeys. These tests should be made for the effect on the endometrium and for toxicity. There are about ten allopregnanes and five normal pregnanes which could be manufactured cheaply and thus made available for testing. Subsequently, arrangements could be made for testing clinically those compounds that prove to be successful in the animal tests. It would be preferable to conduct such clinical tests in regions where contraception is not generally practiced, so as to be sure that an apparent success is not due to concurrent use of other contraceptives, especially in view of the fact that any group which elects to submit itself to the tests will not be representative of the population at large. Of course it would be

necessary to have adequate facilities for checking carefully any side effects if and as they develop from the medication.

A recent report in the literature mentioned in the Appendix describes experiments in which the decidual reaction in rats can be inhibited. This is associated with a reduction of fertility to a level of about 20 per cent. Clearly there may exist many possible avenues of investigation along these lines, two of which are ready for extension to other species and careful evaluation as fertility control agents.

## Termination of Established Early Pregnancy

It is therapeutically possible at this time to reduce fertility by bringing to an end an early pregnancy by use of chemical agents. This has been done in animals and in a limited series of women in whom, it is said, there were clear medical indications for the procedure. The method, described in the Appendix, is effective in a large proportion of cases, but it is at this time fraught with certain limitations which render it of value only under careful and continuous medical supervision. Nevertheless, in a country such as Japan where surgical abortion is an accepted practice for the limitation of births, this procedure might, after careful clinical study, be used as an adjunctive treatment to minimize surgical interference with pregnancy.

## Miscellaneous Methods

### Sterilization by Minor Surgery

Strictly speaking, sterilization by surgical means falls outside the realm of physiological control measures as they are conceived here. However, in order to convey some notion of the range of possible lines of fertility

control, this approach is briefly mentioned here.

It is known that in a few countries there is considerable public demand for surgical sterilization as a means of birth control. Such a means has the advantage of being durable and of freeing the individual from further worry or trouble. It thus seems peculiarly suited to peasant peoples who are not in the habit of using constant vigilance in matters of reproduction but who are in some difficulty from excessive population.

One country in which sterilization is being increasingly used is Puerto Rico. A recent article has this to say:

> "....Evidence of the desire for smaller families is the unusual number of sterilizations performed in Puerto Rico. In 1949, for example, 19.3 per cent of all hospital deliveries on the island were followed by sterilization. In some hospitals the rate was as high as 70 per cent. In many places on the island, hospital bed space for sterilization is a plum held by the local politicos, and both they and the local physicians complain that the demand far exceeds the available facilities."*

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* J. Mayone Stycos and Reuben Hill, "The Prospects of Birth Control in Puerto Rico," Annals of the American Academy of Political and Social Science, Vol. 285 (January 1953), pp. 137-144.

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For the most part, sterilization for fertility control has been practiced with reference to females. It is used to some extent on males, but not frequently as yet. However, since the operation on the male is much simpler (being a case of minor surgery--simply cutting the vas deferens), the possibility of its wide practice must be considered.

One important question with reference to male sterilization is this: can the operation be reversed and fertility restored? The average male is reluctant to lose his reproductive power permanently, especially when he is young. There is always the possibility that his children may die, or that

his wife may die and that he may marry again, his new wife wishing to have children of her own. On this matter it is our understanding that Dr. Vincent O'Connor of Chicago holds that, when the operation is done in a certain way in the first place, it is reversible in a high percentage of cases. It is conceivable that techniques could be developed for performing the operation which will be capable of wide diffusion and use. Undoubtedly, very few voluntarily sterilized males would wish to have the operation reversed, but the knowledge that it could be reversed would be very effective in producing a more favorable attitude towards this means of control.

As in the case of suppressing spermatogenesis, the success of male sterilization as a population control measure will depend in part on the degree of marital fidelity in the population. It is also a type of measure requiring that medical facilities be available, although the amount of time required for the operation is very short and the work could be conducted by mobile units.

It is apparent that this lead is not one that calls for scientific research. Probably there could be improvement, perhaps ingenious improvement, of the surgical techniques for performing it and for reversing the effects of the operation. Such improvement should certainly be considered. But we already have in this lead a method that could be tested in the field. It could be tried in a community in a country like Jamaica or Formosa where governmental cooperation could be secured. As mentioned in previous chapters, such field testing should not be done by the groups sponsoring scientific research, but by some other organization maintaining close liaison with the scientific group. The field test could be designed not so much to test the adequacy of this method for the individual family (for we know already that it is quite sound as a birth control measure) but rather to test the ways

of presenting it to the public and securing popular cooperation.

## Medication Given at Some Point of Menstrual Cycle

It might be possible to prevent pregnancy by giving comparatively small doses of steroid compounds or other agents just prior to the time of ovulation or during the time when the ovum moves through the tube to the uterus. This would be in contrast to steroid medication given steadily throughout the whole menstrual cycle. Such a drug might prevent ovulation, might destroy the ovum on its way through the tube, or might interfere with the implantation of the fertilized ovum in the uterine wall.

Progesterone is believed to have some such effect in certain animals if given on the first day after ovulation. Estrogens given in small doses at the right time with respect to ovulation seem to have some such effect on rabbits. (See Appendix for sources and details.)

It seems likely that no drug could be used in underdeveloped countries which has to be administered precisely at the time of ovulation or at some time fixed with respect to ovulation. The day of ovulation would not be known to most women in such countries; even the charting of body temperature would be out of the question. However, if the drug could be taken between, say, the tenth and the sixteenth day of the menstrual month, and if it were effective if taken on one of these days or else if taken every day from the tenth to the sixteenth day, should the method be rejected offhand as wholly impractical?

Women in most of the areas concerned could not be expected to count the days of the menstrual month. However, the woman could be given little

boxes containing, say, thirty pills--ten of them white, six of them pink, and fourteen of them yellow, for instance. The woman could be instructed to take a pill a day, starting a fresh box each time when the menstrual period comes on. She would first take the white pills until they were all gone, then she would take the pink pills, and finally the yellow ones. The white and the yellow pills would be placebos and the pink pills the active drug.

It is at least conceivable that by giving a dose of stilbestrol, progesterone, or some other steroid about the time of ovulation, pregnancies might be prevented. In the pursuance of this lead, it would seem desirable to design experiments for limited trial prior to setting up a more extended clinical test.

## Toxicity and Side Effect Considerations

In the development of any of the leads for fertility control suggested above, in the Appendix, or to be developed in the future, special consideration must always be given to toxic actions, to individual variation in responsiveness, and to undesirable side effects which are not necessarily noxious. This is one of the major requirements to be fulfilled prior to clinical evaluation of a chemical agent. The principles of toxicity studies are well established and known to competent investigators, and need not be detailed here. The fact needs to be stressed, however, that toxicity studies are expensive, time-consuming, and require adequate laboratory resources.

Depending upon the nature of a substance to be tested, the mode of its development and its potential value as a commercial product, the means of accomplishing toxicity studies will vary. They may be done by private laboratories on a contract basis, by commercial laboratories which have an

interest in fertility control measures, or in a laboratory to be set up and operated as a result of support of the program projected in this prospectus. In any case, a considerable sum of money must be available to afford rapid and effective evaluation as to its acute and chronic toxic or side effects. These certainly involve structural, physiological, biochemical and psychic considerations. The demands of such a program of study cannot be minimized, and it is mandatory to consider them in any competent planning of a fertility control study. It is sometimes objected that physiological fertility control may have harmful side effects. Since to the layman fertility control seems to be "radical" in character, it is vaguely apprehended that there are inherent dangers associated with its use. In a sense, such apprehension is well-founded, because interference with the physiology of reproduction can be difficult to achieve without also affecting the fundamental mechanisms of the body such as the endocrine system. Most of the hormones, for example, which affect the reproductive cycle affect other body functions as well. It follows that the premature or untested use of drugs for physiological fertility control in human beings could be extremely dangerous and should be avoided at all costs. Our proposal, of course, is that a program be undertaken for testing possible agents on animals first and then, if successful, testing them on human beings under carefully controlled conditions. Since "oral contraceptives" are already being discussed in the lay press, the urgency of having systematic testing done as rapidly and thoroughly as possible is very great.

As yet not one of the approaches to fertility control at present envisaged has been adequately tested for toxic and side effects. Some are being tested on laboratory animals with this purpose in mind, but with respect to human beings such experience with drugs as is available with

respect to their effect on the reproductive cycle, relates to the prevention of sterility, dysmenorrhea, or miscarriage rather than the control of fertility. Very little research has been done with the object of fertility control in mind. This means that the minimum dosages required to accomplish this particular goal have not been ascertained, the methods of eliminating undesirable side effects that these dosages could conceivably produce have not yet been investigated, and the reliability and acceptability of each approach have not been established.

Consideration of toxic and side effects forces one to realize that they are not inherent or inescapable sequels to physiological control measures. For example, ovulation normally is suppressed during pregnancy and during most of the menstrual cycle; fertilization does not normally occur in the tube; a second spermatozoon does not enter an ovum after one sperm has already penetrated an egg; implantation is usually prevented when ovulation is not accompanied by the appropriate changes in the uterine lining. Such periodic suppression of fecundity is not only normal; it is implicit in the very nature of the reproductive process in the human being. Furthermore, we know that an absence of fecundity may be perfectly compatible with good health. Men who do not produce viable sperm may be healthy in all other respects and women often fail to ovulate without realizing it and without experiencing any detectable change in their state of health. Finally, we know that hormones and other agents of the type proposed for fertility control are already being used to advantage in various kinds of therapy. In principle, then, the physiologic control of fertility can be accomplished without damage to the individual because the dosages required are within the limits of normal variation in the human organism. A priori, such control involves the utilization of normal elements in nature to accomplish most of the time what nature herself accomplishes part of the time.

## Monetary Outcome of Development of Leads

In conclusion, a statement ought to be made that the working group is well aware of the fact that one yield of research into possibilities of fertility control may be a product or products having large commercial value. Such could come from basic research by private investigators receiving support from the new agency; it could come from a commercial or pharmaceutical laboratory cooperating with the program; or it could come in part from the laboratory which we believe needs to be established to assist in this program of work.

It would be premature for us to endeavor to state what should be done about this matter. It is clearly a matter of policy to be determined by the Trustees of the Board governing the handling of such monies as may be made available to it. This will require deliberation upon and consideration of conditions, the nature of which can not now be defined. It is clear, however, that existing organizations such as the National Research Council, the Carnegie Institution of Washington, various university corporations and government agencies have dealt with these matters. Arrangements made by them may be studied and serve as a guide in the present connection. The essential factor in this is clearly a Board of Trustees who will head an organization planned to be set up, if funds are forthcoming, and which is discussed in Chapter V which follows.

## Chapter V

## A POSSIBLE ORGANIZATIONAL STRUCTURE

On the basis of previous chapters, together with the fuller presentation of the scientific leads in the Appendix, it would seem that the stage has been reached for fruitful program research in fertility control. Our basic knowledge has advanced to a stage comparable to that reached by the development of atomic energy in the spring of 1939. It may very well be that in order to make available within five to ten years methods of fertility control suitable for most underdeveloped countries, all that would be required would be the effort of a small group of men determined to promote this development. No one can say for sure that the effort will be successful, but the chances appear sufficiently good and the importance of the problem sufficiently great to justify the undertaking.

In thinking of men who would be effective in such a group, one must not think only of experts in the field of science. Past achievement in any field of human activity, coupled with a deep conviction that an early solution of this problem is important and the determination that the job shall be done, ought to be the guiding point of view. Whether or not such a group of men working together for a common goal wish to formalize their association -- say, by forming a committee -- is of secondary importance. It is of primary importance that they be clear about the various aspects of the job to be done. These aspects are as follows:

1. To see to it that as soon as a new method becomes available it should be clinically tested -- if necessary, abroad;
2. To assure so far as possible that basic research in the field of mammalian fertility should not lag for lack of funds;

3. To see to it that such leads as emerge be pursued immediately by carrying out the indicated sequence of experiments. A rapid evaluation of possible leads for fertility control will be of paramount importance.
4. To encourage and, if necessary, give financial assistance to promising experiments in the field that are being carried out in any established institution of research, whether in the United States or abroad;
5. To enlist fresh talent in the service of the task, preferably from among young post-doctoral students who are convinced of the importance of the issue and determined that the job shall be done;
6. To diffuse and stimulate interest abroad so that the program becomes international rather than purely American in scope.

Outline of the Task

It appears probable that if an adequate program were set up, we should have available within a period of five years some method for reducing fertility which is reasonably effective and free from major health hazards, not prohibitive in cost, and acceptable in at least some of the major overpopulated areas. This does not mean that this method will be fully satisfactory. It is more likely that the first acceptable method which we may be able to put forward will subsequently be replaced by successively better methods. In this sense, it is likely that the problem of finding methods for reducing fertility will be with us for a generation, even though usable methods may become available rather soon and may have an appreciable effect within ten years on the population growth in many of the overpopulated areas.

While finding methods of reducing fertility is our immediate concern, we cannot be indifferent to the plight of some 3-4 million childless couples in the United States who may desire to have children but are unable to have them. Since, however, there are numerous and varied factors that may cause infertility, it is probable that progress in this field cannot be made as sweeping as it may conceivably be made in the field of reducing fertility. Consequently, insofar as the proposed program would lend support to this activity, it should probably do so in behalf of basic research in the general field of mammalian fertility. A rather modest sum might be usefully spent each year for supporting the work of men of the highest quality who are now working in this general field of research. It might be advisable to expend larger funds later on, but only in the measure in which, with the increase of our knowledge, new leads emerge upon which program research may be based.

The Scope

In the present chaotic state of affairs in the field we are discussing, one could probably do useful work even though operating on a shoestring. By wisely spending, say, $50,000 to $100,000 a year, some useful work in following up critical leads and clinical testing could be farmed out. A small committee with a full-time research director could possibly take charge of such an operation.

However, in order to have fair assurance that the job will actually be done and that it will be done in reasonable time, the program should be on a larger scale and on a more permanent basis. Perhaps we should think at this time in terms of setting up an organization, which may be called something like "Organization for the Study of Mammalian Fertility." This organization should be designed to remain in operation for twenty-five

years but it ought to operate on the basis of a five-year plan. It should begin to operate full-scale as soon as the necessary funds can be secured for a period of five years.

The Means

The success of the operation of this organization will largely depend on the sound judgment of the scientists who take on the responsibility for deciding what lines should be pushed and how fast they shall be pushed. Before the job was done, one may have had to spend as much as $2,500,000, or an average of half a million per year. This is a large amount of money to spend, but unless it is spent wisely it will make very little impact. It is contemplated that the hard core of scientists who take upon themselves the responsibility of pushing this development may consist of about twelve distinguished scientists who serve on a part-time basis as "Associates" of the organization and about six scientists of PhD. rank, probably in the twenty-five to thirty age group, who serve on a full-time basis as the members of the staff of the organization. The Research Director of the organization, and perhaps also its Director, if he is a scientist, will presumably not belong to the twenty-five to thirty age group, but will be closer both in age and in stature to the group of Associates.

The Associates will, in general, be men of much greater experience, knowledge, and perhaps also ability than the younger group represented by the full-time staff. Many may have worked in the field for a long period of time. Experience of this sort is both an asset and a liability. Men of experience in the field are likely to be more or less committed to certain approaches. They will know all the details in their own field but have only slight acquaintance with work in adjacent fields

and usually little inclination to buckle down and go in detail over the work of others.

The younger groups represented by the full-time Research Staff will lack the experience and the breadth of knowledge of the Associates but if they are really first-class men -- as they must be if the organization is to be successful -- they will be free, and for some time remain free, of any commitments to any particular approach to the problem. They will be willing to push any approach which appears promising and willing to undertake any experiment that in their judgment is needed. In this way existing gaps may be filled in fast, as they must be if we are to have a rapid and orderly development in the field.

The Associates and the full-time staff will have to be kept in close touch with each other. This will automatically evolve from the way the organization is set up to operate. The Associates must be willing to devote a considerable fraction of their attention to the organization's activities for stretches of a year or two at a time, even though this will have to be done on a part-time basis. By arranging for this on a rotating basis the load of the work could be fairly evenly distributed on all the Associates in the long run.

The salaries of the full-time scientific staff of the organization, the expenses and compensation paid out to the Associates, and secretarial help for both the scientific staff and the Associates might represent an expenditure of $100,000 a year.

Clinical Testing

One of the functions of the organization will be to design and arrange for clinical tests of drugs which have been developed to the point where there is reason to believe they are effective in reducing

fertility and are free from at least acute toxic effects.

Because most of these drugs may not be foolproof in the sense that a pregnancy might ensue where none was desired, clinical testing in the United States would be almost impossible. At best it would be a slow and cumbersome process. If we want to make progress fast, such drugs will have to be tested in areas where we can be certain that no other methods of contraception are ordinarily used concurrently with the drug being administered. One may think of a country like Puerto Rico, or perhaps Jamaica, where the government adopts a friendly attitude to the problem of fertility control, where simple clinical facilities might be set up in rural areas, where the population is sufficiently intelligent to report promptly to the clinic symptoms that might appear during treatment, and where the wage level is low enough to permit us to induce the patients to report on schedule at the clinic by paying them a small fee of their visits. A test carried out under these conditions with three hundred selected couples for a period of eighteen months might be sufficient to establish the effectiveness of the drug beyond reasonable doubt. It might take a test based on one thousand selected couples to establish the minimum dose that can be considered reasonably effective and for striking a sound balance between sufficient reduction of fertility and tolerable cost of medication. Clinical testing of this sort is an art and one of the first tasks of the organization would be to develop this art.

The organization itself, however, would not conduct clinical tests; such tests should rather be placed in the hands of other appropriate agencies. In Puerto Rico, for instance, the obvious choice would be the Medical School of the University of Puerto Rico. The organization

may evaluate the knowledge available about the drug which is considered ready for clinical testing; it may set down the scientific criteria which the tests would have to meet and may, in cooperation with the school or agency conducting the work, set up the blueprint of the test; it may also provide, in full or in part, the funds which are required.

The cost of testing one drug on three hundred to one thousand couples might be somewhere between $30,000 and $60,000. If the drug is one in which a commercial company is predominantly interested, the organization might arrange for the participation of the company in the cost of the tests.

The Development of Leads

The development of existing leads to the point where they are ready for clinical testing -- as well as the finding of new leads -- will require close collaboration of the organization with scientists working in the general field of mammalian fertility in a number of different laboratories in the United States. There are good men working in the field of mammalian fertility and other relevant fields in a number of laboratories in the United States and other countries and research programs should be farmed out to them whenever possible. For this procedure to be successful it would be necessary both to win the cooperation of these men and to provide them with the funds needed for the execution of the experiments.

Many experiments can be carried out on rats and rabbits, but other experiments have to be carried out on monkeys whose physiology of reproduction resembles in important respects that of the human. There are today very few laboratories where major experiments having a direct bearing on our problem are carried out on primates. There are, however,

some other laboratories which are equipped to work with monkeys and which are staffed with good men who might perhaps be convinced that they ought to orient more of their work in directions which may lead to the development of new methods for reducing fertility.

In the past, the main interest of workers in the field of mammalian fertility was not focused in the future. We can try, however, constantly to keep before their eyes the importance of the issue and we can try to create a climate of opinion favorable to program research in this field.

The quantity of program research which our best laboratories can accommodate is limited since their main responsibility is to advance our basic knowledge and to educate scientists. Nevertheless, we may expect the cooperation of these laboratories to be important and, depending on our success in stimulating their interest in our central issue, we should be able to spend on experiments which may be farmed out to them a fairly substantial sum.

It is difficult to estimate at this time how much money could be really usefully spent in this manner, but it would seem desirable to have available for this purpose, including the sums to be spent for clinical testing, about $200,000 per year. It seems likely that less will be spent in the first year or two of the organization's operation than in the following three years, and it should be possible to accumulate reserves in the first two years which could be used to bolster the budget of the subsequent three years.

But no matter how successful such a general plan of farming out the bulk of the research may be, there will always be gaps which cannot be filled in this manner as fast as is necessary, if they can be filled at all. Many experiments, some of them previously performed by others with controversial results, will have to be done by the organization itself.

This makes it necessary for the organization to have a laboratory of its own, operated by the organization's full-time research staff. One would hope that no more than one-third of the research budget, i.e., less than $100,000, will have to be spent for running this laboratory and, correspondingly, the laboratory should be kept small, comprising about 15,000 square feet floor space. It might be possible to rent such a laboratory or to equip an existing building, but if we assume that ultimately a laboratory will have to be built, the cost of building and equipping might amount to $300,000.

The laboratory might be located near a university or medical school and have some ties with such a school. In this respect, the example set by the relationship between the Carnegie Embryological Laboratory of the Carnegie Institution of Washington and Johns Hopkins might be followed. The physical proximity of a medical school would offer great advantages. Apart from library facilities, which need not be duplicated, the research staff would derive stimulation from their contact with the faculty of the school. Locating the laboratory near the College of Physicians and Surgeons of Columbia University is one possibility; locating it near the Cornell Medical Center is another which deserves being explored. Moving the laboratory out of New York City but keeping it in the vicinity would also have certain advantages which would have to be weighed.

Basic Research

The program should, it is felt, give modest support to the furtherance of nonprogram (basic) research in the general field of mammalian fertility. This would be done in the hope that such research would contribute both to remedying infertility and to the emergency of new leads in fertility control.

The best method for supporting basic research of this character would probably be by means of grants-in-aid. Such grants should not be given for "projects", but rather they should be given to the best men working in the field, without any strings attached. It ought to be possible to use such grants at the discretion of the investigator for equipment, technical assistance, or for fellowships for graduate and post-graduate students working in the laboratory of the investigator. It is estimated that if $50,000 per year were distributed in the form of such grants, this would appreciably accelerate progress in the field of mammalian fertility. It would also constitute another link between the organization's staff and the best biological laboratories.

Research Committee

The funds disbursed for clinical testing and other research that is conducted outside of the laboratory of the organization might be disbursed by a "Research Committee" of perhaps ten men, half of whom would be drawn from among the associates of the organization (who serve on a part-time basis) and the other half from the full-time research staff of the organization. The budget of the research committee would be separate from the budget of the organization's own laboratory and would be fixed from year to year by the board of directors of the organization.

The Research Committee might spend for work which is farmed out, including clinical testing, $200,000 a year.

Faculty of the Laboratory

The faculty of the organization's laboratory would be composed of the full-time research staff of the organization, perhaps six in number, and three outside members drawn from the twelve associates who would

take turns in serving on this faculty. The salaries of the research staff and the compensation of these associates would be comprised in the $100,000 item already mentioned for the staff of the organization, including the director and secretarial personnel.

It has already been mentioned that the cost of building and initially equipping the laboratory would run to approximately $300,000, being a nonrecurrent expense. In addition, the cost of operating the laboratory, not including the salaries for the scientific research staff, might amount to $100,000 per year.

Committee on Grants-in-Aid

The grants for nonprogram research may be distributed by a small committee, the "Committee on Grants-in-aid", made up of perhaps six scientists. The majority, i.e., at least four out of the six, should be drawn from a panel of distinguished scientists. The members of the former National Research Council Committee on Human Reproduction might be asked to serve on the panel and might rotate on the committee on grants. No scientist who intends to apply for a grant, however, should serve as a member of the committee. No more than one or two members of the committee may be drawn from the full-time scientific staff of the organization. It has already been stated that $50,000 per year might be spent *in toto* for grants by this committee.

Board of Trustees

It is assumed that the organization would be headed by a board of trustees to whom the director would be responsible.

Estimate of Costs

A sketch of the organization for conducting the proposed research program has now been given. In connection with each part an estimate of the probable cost for a five-year period has also been given. In order to arrive at a total proposed budget we now list the major items of expenditure. This listing is as follows:

| | One Year | Five Years |
|---|---|---|
| For salaries of full time scientific staff, compensation of Associates, and secretarial staff | $100,000 | |
| Operating expenses for a laboratory of 15,000 square feet | 100,000 | |
| Disbursement by Committee on Research | 200,000 | |
| Disbursement by Committee on Grants-in-Aid | 50,000 * | |
| Administrative Overhead | 50,000 | |
| | $500,000 | $2,500,000 |
| Initial Investment for Laboratory and Equipment | | 300,000 ** |
| Special Equipment | | 50,000 |
| | | $2,850,000 |

If changes should be made in the items with an asterisk, as detailed below in the footnotes, the total cost would be $2,410,000.

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* In case of necessity, this is one item which could be dropped from the program, since a basic research program of the sort envisaged under this head might be properly supported by some other organization. An additional saving of $5,000 per year overhead would ensue.

** In case a building were rented for laboratory purposes, the expenditure for this item might be reduced to $125,000 for the five years, assuming an annual payment of $25,000 for rent.

# APPENDIX NUMBER ONE

## Specific Leads to Physiologic Control of Fertility

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## APPENDIX NUMBER 1

Lead # 1. Suppression of Fertility by a Steady Administration of a Steroid (or its Analogue) to the Female.

It is believed that ovulation can be suppressed as long as desired by continuously giving to the patient an estrogen, for instance, stilbestrol. The minimum dose which will have such an effect seems to be unknown and it is also difficult to state at the present time whether such a minimum dose would affect the menses. If the dose necessary is above a certain minimum, the estrogenic side effects may make the method unacceptable.

Roy Hertz mentioned that the other obvious estrogens have shown in animal experiments that their estrogenic action goes parallel to the action on the pituitary, so that nothing would be gained by using the weaker ones from among these estrogens. Nevertheless, it is conceivable (Hisaw) that some compound belonging to this group will be found which will have a strong effect on the pituitary and a weak estrogenic effect, and that such a compound might be useful for our purpose.

It appears that progesterone injected in amount of 250 mg. will suppress ovulation (Hertz). It has been given for therapeutic purposes in large doses over long periods of time to both men and women with no toxic effect. In the case of women, however, when medication is stopped there is withdrawal bleeding from the uterine wall. It remains to be determined how low a dose of progesterone will be sufficient to suppress ovulation and whether such a dose will interfere with the menses. If, for instance, 25 mg. per day injected were to prove effective, the cost

of this type of therapy might be low enough to be tolerable. (Progesterone could be obtained today in large quantities at 50 cents per gram so that the cost per woman per year would amount to less than $5.)

Whether progesterone itself is effective if taken orally is not really known, but it could be taken in the form of buccal tablets (i.e., tablets placed between the jawbone and the cheek which are absorbed through the mucus membrane in about 15 minutes). It is also conceivable that progesterone can be administered in the form of vaginal suppositories (Pincus; animal experiments show progesterone to be as effective by this route as injection). Ethanyl testosterone can replace progesterone and can be taken orally, but it is about one-fifth as effective (Roy Hertz) as injected progesterone. This compound could easily be made from progesterone (White). Ethanyl-norprogesterone is about three to four times as active when taken orally as ethanyl testosterone (Roy Hertz) but it might not be possible to make it at a low price (White).

Progesterone administered by injection in doses of 250 mg. daily will cause occasional uterine bleeding (withdrawal bleeding may follow within 48 hours after ceasing to take progesterone). Whether such withdrawal bleeding would still occur on a progesterone regimen which represents a minimum dose sufficient to suppress ovulation, remains to be seen and might determine whether this method can be recommended in underdeveloped areas.

Compounds of the allopregnen and pregnane series can be made fairly cheaply and some of them might suppress the pituitary and be free from

any effect on the endometrium of the uterus that would lead to withdrawal bleeding.

Ten compounds of the allopregnen series which are particularly easy to make are ready to be tested, and five compounds of the normal pregnane series (White). It would take about four months for each compound to be tested on rats and rabbits and to determine the dosage at which ovulation is inhibited. Such a test would cost about $1,500 per compound (Pincus).

One may now proceed:

1. to determine the dose at which compounds related to progesterone will suppress ovulation in the rat and the rabbit;
2. to have large-scale clinical testing of progesterone and such related compounds for which the dose has been approximately determined in the rat and the rabbit;
3. to determine the effectiveness of different routes of administration in clinical tests.

Lead # 2. Lithospermum ruderale.

It has been reported that lithospermum ruderale has been used by the Shoshone Indians in the southwest to reduce fertility of the female, and experiments carried out on female mice have, in fact, shown that aqueous extract prepared from the root, flower and seed of this plant will suppress the reproductive cycle without injurious side effects. * As soon as medication is stopped, the animals become pregnant.

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* Paul A. Zahl, Proc. Soc. Exp. Biol. Med., 67, p. 405, 1948.

Clinical experimentation on humans has been started in England (where they so far have data on just a few human subjects**).

One may now proceed with:

1. experiments on primates with standardized extracts of the plant;
2. clinical research, preferably in areas where no other method of birth control is practiced, but where clinical facilities are available to watch for possible undesirable side effects from the drug.

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** Nature, 170: p. 274, 1952, Wiesner and Yudkin.

Lead # 3. Calladium seguinum.

This South American plant if fed to male or female rats will lead to changes which usually accompany castration. But no castration cells or other histological changes are found in the pituitary. *

It would seem to be advisable before going any further to determine whether the degree of the effect can be controlled by standardizing the dosage so that fertility is suppressed without suppression of either the secretion of estrogens in the female or androgens in the male and to determine whether administration of the drug over a long period of time during which fertility is suppressed will be followed by complete recovery when administration of the drug is stopped. After this one might move on to experiments on monkeys and to clinical tests.

At this time it is not recommended to set up a specific research program based on this plant.

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* G. Madurs and F. R. E. Koch, Z.f. Die Gesamte Exp. Med., 107, p. 68.

Lead # 4. Prevention of Pregnancy by Steroids which Compete with Progesterone in its Effect on the Endometrium of the Uterus.

From a physiological point of view, we would have a very desirable method of fertility control if we could find a steroid which prevents implantation of the fertilized egg by its direct action on the endometrium of the uterus. A chemical analogue of progesterone which would compete with progesterone in its effect on the uterus or which otherwise would directly affect the uterus appears to be a possibility. Dr. Hisaw finds in the rat that certain compounds of the pregnane series will interfere with the development of decidual tissue and in this sense will compete with progesterone and prevent pregnancy. We cannot a priori expect man to respond the same way the rat does, and experiments on monkeys along these lines would be helpful.

Work along this line ought to be pushed vigorously because it is conceivable that a compound may be found which is effective and which has, apart from the effect on the endometrium of the uterus, no appreciable general physiological effect. Such a drug would appear a priori more desirable than drugs which suppress the gonadotropic hormone secretion of the pituitary.

There are about ten allopregnens and five normal pregnanes, which could be manufactured cheaply, available for testing.

One may now proceed:

1. to the testing of such steroids in laboratory animals, including monkeys, for their effect on the endometrium of the uterus, and for possible toxicity;
2. to the clinical testing of such steroids in geographical areas where contraception is not generally practiced and where clinical facilities can be set up to check on the effects of the drug.

Lead # 5. Small Doses of Steroids Given at Mid-month.

It may be possible to prevent pregnancy by giving comparatively small doses of a steroid compound just about the time of ovulation, or during the time when the ovum moves through the tube to the uterus.

Progesterone is believed to have such an effect in certain animals if given on the first day after ovulation (Cassidy, Willet--remark by Dr. Carl Hartman.) Estrogens given in small doses at the right time with respect to ovulation seem to have such an effect on rabbits (unpublished experiments of Dr. Csapo in Corner's laboratory. Whether the effect in Dr. Csapo's experiment is due to an interference with the transport of the ovum through the tube, or whether there is some direct toxic effect on the ovum (Reynolds) is not known with certainty.)

No drug could be used in underdeveloped countries which has to be administered precisely at the time of ovulation or at some time precisely fixed with respect to ovulation. The exact time of ovulation is not known and in underdeveloped areas even the charting of body temperatures is out of the question. However, if the drug could be taken between, say, the tenth and the sixteenth day of the menstrual month, and if it were effective when taken either on one of these days or else if taken every day from the tenth to the sixteenth day, should the method be rejected offhand as wholly impractical?

Women in most of the areas concerned could not be expected to count the days of the menstrual month. Szilard thinks, however, that the woman could be given little boxes containing thirty pills, ten of them white, six of them pink, and fourteen of them yellow, for instance. The woman could be instructed to take a pill a day, starting a fresh box each time when the menstrual period comes on, and first to take the white pills until they are

all gone, then to take the pink pills, and then to take the yellow ones. The white and the yellow ones are placebos, and the pink pills are the drug.

It is conceivable that by giving a dose of stilbestrol, progesterone, or some other steroid, about the time of ovulation, to the women, pregnancies might be prevented.

One may now proceed to:

1. make tests on monkeys;
2. make clinical tests in underdeveloped areas where no other methods of birth control are practiced.

Lead # 6. Anti-histamines.

Unpublished experiments by Dr. M. C. Shelesnyak, Weizman Institute of Science, Rehobeth, Israel, indicate that in mice fertility may be reduced from between 95%-100% to 20% by certain anti-histamines administered at the time when the fertilized ovum reaches the uterus (Reynolds). It is assumed that the action of the drug interferes with the implantation of the egg in the endometrium. The paper is im press in the American Journal of Physiology.

If it can be established that the anti-histaminics in fact interfere with fertility in animals, one may then proceed to experiments which may be carried out on monkeys with different anti-histaminics and clinical experiments which may be made in areas where no other method of birth control is practiced, using drugs which have been adequately tested for toxicity.

At this time no recommendation is made to set up such a program.

Lead # 7. Immunization with Sperm.

A. Immunization of the Male

Male guinea pigs can be immunized against sperm of the same species using adjuvants. The spermatogenesis of such guinea pigs ceases for a long period if not permanently. There are histologic changes in the testis but no other organs appear to be affected. *

One might ask whether this is a lead not only to permanent but also to temporary sterilization for the human male. The odds for permanent sterilization appear to be rather good if we may extrapolate from the guinea pig to man. Such extrapolation, however, is highly tenuous, because the guinea pig tends to be in a class of its own when it comes to immune reactions. Moreover, immunological reactions may vary so greatly among individuals that it may prove impossible in man to determine the dosage which will cause temporary rather than permanent sterility.

Dr. Freund's experiments on guinea pigs were made using paraffin oil and myco-bacteria as adjuvants. In order to be in a position to control possible local reaction at the site of injection, in applying the method to humans, one would want to use intracutaneous injections (Freund).

B. Immunization of the Female

The question arises whether using the same method for immunization of the female of the species will prevent conception due to the secretion of antibodies in the tube, the uterus, or the rest of the genital tract.

The following points are now ready for investigation:

1. Can the female be immunized with sperm with a result of a drop in fertility? This point can be tested by very simple experiments on the usual laboratory animals.

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* Based on information presented by Dr. Jules Freund.

2. If the answer to (1) is positive, is there any tissue damage in these animals due to cross-immunity?
3. If the investigation in (2) shows no damage to the animal, it should then be extended to monkeys.
4. If there is no damage demonstrable in monkeys, clinical tests may be made.

Lead # 8. Local Application of Antibodies.

According to Dr. Jules Freund, antibody titer to sperm reaches in the guinea pig a level at which the purified antibody may be diluted in the ratio of 1:2500 and still immobilize sperm. The question arises as to whether such high titer antibodies if placed in the vagina might not prevent conception for an appreciable period, say perhaps a week. In order to keep the antibody in the vagina, some porous sponge-type mass which is filled with antibody might perhaps be used.

Dr. Folsome points out that if a non-human immune serum is used and if the antibodies were resorbed from the vagina, the patient would become sensitized to the foreign protein. He also points out that, so far, no sponge has been developed which could be left in the vagina for more than 48 hours without causing irritation.

The research necessary to see whether this is a useful lead is rather simple, but no consensus has been reached so far as to whether such research should be encouraged.

Lead # 9. Phosphorylated Hesperidin.

Phosphorylated hesperidin will reduce fertility in rats, according to a paper published in Science,* from 80% to 20% when administered to the female rat in a dose of 20 mg/kg intraperitoneally or 100 mg/kg orally.

Dr. Benjamin F. Sieve, a medical doctor in Boston, has for a number of years administered this drug to married couples, giving the drug to both husband and wife orally in amounts of about 300 to 400 mg. per day. His results were published early in October in Science.

He claims that he was able to prevent conception in the couples so treated. All his patients had had children before, and when treatment was stopped, practically all of them became pregnant again. In toto, he had about 130 pregnancies which ensued when the treatment was discontinued. He claims that in all cases the women became pregnant within three months after stopping of the treatment, which is rather astonishing.

While he has a number of patients who have been under control for fairly long periods of time (longer than eightmonths), his data do not indicate how much time elapsed between the birth of the last child and the beginning of his control period, whether the woman lactated following childbirth, and for how long she continued to lactate during the control period.

It is not possible to evaluate the data which Dr. Sieve presents in this paper. His experiments indicate, however, fairly convincingly, that the drug is not toxic and makes the following program research appear to be desirable:

1. Whether or not the drug is effective may be determined by interviewing about twenty-five of Dr. Sieve's patients selected from

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* Science, 115 (2989): 402, April 11, 1952, "Effect of Phosphorylated Hesperidin, a Hyaluronidase Inhibitor, on Fertility in the Rat."

his records in order to establish (a) whether they have in fact not used any other contraceptives; (b) whether they did or did not become pregnant while they were still continuing to take the drug; and (c) which of his patients lactated during the control period.

2. If the investigation under (1) indicates that the drug is effective, the chemical process of producing phosphorylated hesperidin should be improved to the point where it becomes reproducible. The drug is now being made in experimental batches by the National Drug Company in Philadelphia. Dr. Martin, Research Director, informs us that the individual batches greatly differ in their physiological activity so that it becomes necessary to test each batch on experimental animals. Phosphorylated hesperidin is an inhibitor of hyaluronidase and the test used is based on the influence of the drug on the spreading of injected dyes in the skin of rabbits.

3. Large scale clinical tests might be set up outside of the United States in an area where one may be sure that the patients do not use any method of birth control. Three hundred couples might be selected within the area of the clinic and paid a small sum, perhaps up to thirty cents a day, for coming to the clinic every day and taking the drug in the presence of an officer of the clinic for a period of a year. If such an experiment were carried out in a normally highly fertile population, it should show within a year whether the drug is effective. A control experiment using placebos would, of course, be desirable, as stressed by Dr. Tislow.

When the chemical process is standardized, this drug should be cheap, since hesperidin is present in great abundance in lemon and orange peel.

If this drug is really effective, because of its low cost, lack of taste, and apparent lack of toxicity, it could be administered in drink or food, and special brands of such drink or food could be made available at low cost by the interested governments.

Lead # 10. Aminopterin.*

In humans, a fourteen-day old embryo, i.e., an embryo at the time when menstruation is missed for the first time, will almost certainly abort if a dose of 6-8 mg. of aminopterin is given in two days in the form of tablets three times a day. If the embryo is six weeks old, i.e, at the time when the second period is missed, 12-15 mg. of aminopterin given in 4 days in the form of tablets three times a day will almost certainly cause abortion. The above dosages relate to women weighing between 110 and 140 pounds.

This medication does not cause any permanent damage to health; 6-8 mg. of aminopterin may cause a temporary reduction of the white count from 9000 to 7500.

Should abortion not be successful and the third period be missed, it would then be necessary to resort to surgical abortion, because medication by aminopterin will lead to malformation in the child.

Vitamin C and folinic acid may be given following aminopterin therapy in order to hasten recovery.

Aminopterin is made by Lederle and is available for clinical use.

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* The factual data presented here are based on information supplied by Dr. John B. Thiersch of the University of Washington.

In a country like Japan where abortion is legal and an accepted form of birth control and where there are surgical facilities available to take care of those cases where the chemical abortion fails, animopterin might find wide usage. The same would not hold true in India. There, there are not sufficient surgical facilities available to take care of women in whom chemical abortion failed, and also there may be an aversion to the general concept of abortion.

The following points are now open to investigation:

1. What fraction of those who attempt abortion by aminopterin do ultimately require surgical abortion?
2. Are other analogues of folic or folinic acid preferable to aminopterin?
3. Are analogues of other vitamins preferable to folic or folinic acid analogues, or usable in conjunction with folic or folinic acid analogues?

Lead # 11. Abortion by Causing Hemorrhage in the Placenta

Paul A. Zahl and Clara Bjerknes have shown * that abortion may be caused in rabbits and mice by injecting non-lethal doses of certain bacterial endotoxins. The abortion is due to an effect on the blood vessels of the placenta which leads to hemorrhage.

Not enough discussion was devoted to this method of abortion to reach consensus as to whether this approach deserves further attention.

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* Proc. of the Soc. for Exp. Biol. and Med., 54:329, 1943; 56: 153, 1944.

Lead # 12. Micro-Biological Method.

It is known that certain females who are sterile carry certain micro-organisms in the genital tract and that upon elimination of these micro-organisms these individuals become fertile. One may ask whether it would be possible to cause sterility by cleaning out the normal flora in the genital tract with a massive dose of a micro-organism which causes sterility. The question arises how long such a micro-organism would maintain itself before it is replaced by the normal flora. Dr. Seeger Jones in Baltimore is now experimenting with a non-pathogenic fungus which was found to be the cause of sterility in two of her patients, and the outcome of her experiments should be followed.

Program research in this field is now possible in the hands of gynecologists who work in cooperation with micro-biologists:

1. Non-pathogenic organisms might be taken from patients who are sterile and might be (a) tested in vitro for their interaction with sperm, or (b) transmitted to normal women to see if they can maintain themselves and cause sterility;
2. Other micro-organisms not so far found in the vagina which are non-pathogenic to animals including monkeys and which do interact with sperm in vitro might be introduced in the vagina to see (a) whether they can maintain themselves for a reasonably long period of time, say a week or a month, and (b) whether they cause sterility.
3. Dr. Folsome suggested that the micro-organisms might elaborate substances that could be extracted and concentrated. If discovered, these extracts would have advantages over the inoculation with live organisms.

Lead # 13. Suppressing Spermatogenesis with Testosterone.

In spite of conflicting reports, the weight of evidence seems to indicate that a steady administration of testosterone will suppress spermatogenesis. Testosterone presumably affects the pituitary, and thus interferes with the secretion of one or more of the gonadotropic hormones. The suppression of spermatogenesis is reversible, and when administration of testosterone is stopped, spermatogenesis reappears undiminished.

It is estimated that testosterone bought in large quantities might become available within two years at a price of perhaps 50 cents per gram (today it could be made available for perhaps $1.50 to $2.00 per gram if purchased in large quantities.)

Testosterone can be administered in pellets which may be placed between the jawbone and the cheek and which are absorbed in about fifteen to twenty minutes. Assuming that 25 mg. per day had to be used (transmucosal administration), it would take about 10 grams per year or, at a price of 50 cents per gram, $5 per family to practice this method of birth control.

The effects of testosterone on the libido in males aged 20 to 50 might represent an undesirable side effect. There is some concern that there might be an increase in libido without a corresponding increase in potency (Sollins). If this should be a frequent occurrence, the undesirable psychological consequences to the individual will have to be weighed. There is also some concern that there might be a hypertrophy of the prostate. (Hertz).

Program research:

1. Find out beyond reasonable doubt whether testosterone in a given

dose will in fact eliminate spermatogenesis for as long a period of time as may be desired, and if there is complete recovery when administration is stopped after several years of therapy. Clinical tests of this sort may be conducted in the United States with volunteers who have had several children and do not expect to want another child.

2. An inquiry may be made whether testosterone could not be replaced by cheaper chemical analogues, in the same way in which natural estrogens can be replaced by stilbestrol. The first question to be looked into here is how much research had already gone into an attempt to find a cheap substitute for testosterone, and how good were the men who made such attempts.

Lead # 14. Suppression of Spermatogenesis with Progesterone or Related Compounds.

Progesterone has been given in large doses over a long period of time to men without any known side effects. No attempts were made, however, to determine whether spermatogenesis was affected. It is a priori likely that progesterone given in a sufficiently large dose over a long period of time will by way of the pituitary affect spermatogenesis. Szilard thinks, therefore, that one cannot afford to overlook the possibility that progesterone may reduce fertility by affecting spermatogenesis without appreciably affecting the inner secretory function of the testis. With respect to the administration of progesterone, see Lead # 1.

Dr. Hisaw emphasized the possibility of using some compound of the pregnane series rather than progesterone for suppressing spermatogenesis.

1. One can now proceed to clinical testing of the effect of progesterone on spermatogenesis. This can be done in the United States in clinics where progesterone may be administered therapeutically in rheumatoid arthritis, or in experiments made on volunteers who are willing to collaborate in research aimed at reducing fertility.
2. One can study in animals, including monkeys, the effect on spermatogenesis of progesterone and compounds of the pregnane series.

Lead # 15. Cutting of the Vas deferens (Vasectomy).

This involves very simple surgery and the one remaining technical question involved is whether vasectomy can be performed in such a manner as to be reversible. It is our understanding that Dr. Vincent O'Connor of Chicago holds that if the vas is cut in a certain region (which is not necessarily the most convenient region to reach), the operation is reversible in practically 100 per cent of the cases.

The role that vasectomy might play depends on whether there is a high degree of marital fidelity as in India or a high degree of promiscuity as in Jamaica.

In India, vasectomy would be as effective from the point of view of population control as the sterilization of women, and might have the advantage of reversibility and avoidance of abdominal surgery. Motivation for the male to undergo vasectomy may, however, not be as strong as the motivation for women to undergo sterilization.

In Jamaica, on the other hand, women might give preference to men

who are known to have had a vasectomy, thereby supplying a motivation for vasectomy which is non-existent in India. But in view of the prevailing promiscuity one might ask what fraction of the male population may have to undergo vasectomy before there is an appreciable effect on the birth rate.

Dr. O'Connor's views will have to be evaluated before recommending further clinical research for the purpose of establishing "reversibility" beyond reasonable doubt.

Lead # 16. Active Immunization of the Female against Proteins of the Placenta or Umbilical Cord.

It is claimed by Dr. Alexander Langer, at present at Mt. Sinai Hospital in New York, that animal experiments previously carried out by him in Cuba showed the following:

Female mice and rabbits immunized against Wharton's Jelly extracted from the human umbilical cord will show reduced fertility.

The thought behind this approach is the following: if the placenta or the umbilical cord should contain a specific protein which, when injected into the same species will cause the formation of antibodies, then a female who has been so immunized might be infertile because the interaction of her circulating antibodies with the placental proteins might either prevent implantation or cause early abortion.

Langer's experiments ought to be repeated * under carefully controlled

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* Dr. Alan Guttmacher has informed us recently (March 24, 1953) that Dr. Langer has confirmed his original results in experiments at the Mt. Sinai Hospital. The pregnancy rate in mice in the experimental series is 25 per cent as opposed to 65 per cent in the controls. Independent verification is projected.

conditions to see if his results can be duplicated. If they can, it will be necessary to investigate whether there isn't some damage to some of the organs of the "mother" due to cross-immunity. If no such damage can be detected, the experiments would have to be repeated in monkeys before going over to clinical testing.

If Langer's experiments can not be repeated we should reevaluate his general approach and try to decide whether to proceed to work with isolated proteins of the placenta, or drop this whole approach to the problem.

Lead # 17. Ligation of the Tubes.

In Puerto Rico, after a woman has had a sufficient number of children and delivers a baby in a hospital, the tubes are quite often ligated immediately after the delivery of the baby. This involves abdominal surgery which, however, is particularly easy if performed immediately after childbirth, and the patient recovers from the operation by the time she recovers from the delivery.*

This method of sterilization is irreversible. It can be significant only in countries where an appreciable fraction of the babies is delivered in hospitals. Puerto Rico is one example, Japan might possibly be another.

Kingsley Davis believes that irreversibility is not a major obstacle to widespread use of the method, whereas Hutchinson and Szilard have misgivings about this point. They argue that even though a woman may have

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* The above statement is based on information supplied by Dr. Howard Taylor of the College of Physicians and Surgeons, New York.

had as many children as she wants to raise, all of her children might die (particularly in countries with high child mortality.) Being deprived of all hope of having further children might then represent a major calamity for a woman.

There is no need for us to resolve the above-indicated divergence of opinion since the surgical procedure involved is well worked out and no developmental program is therefore called for in any case.

Lead # 18. Ligation of One Tube Only.

In a country like Japan where abortion might become the predominant method of birth control, particularly if surgical abortion can be replaced by the use of aminopterin (or better drugs to be developed in the future), one might want, according to Szilard, to recommend ligation of one tube at the time when the first child is born.

If one tube is ligated, both ovaries continue to function normally but only half of the eggs produced will have a chance of being fertilized and implanted in the uterine wall. Assuming that abortion is practiced as the preferred method of birth control, with one tube ligated, the interval between two successive abortions would double. If no birth control of any kind is practiced, in the case of the most fertile group, i.e., the group of young mothers, the mean interval between two successive pregnancies would be lengthened by about four months.*

Kingsley Davis thinks that this method has no chance of acceptance because people even in underdeveloped areas either want or do not want

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* This figure is based on Dr. MacLeod's statement relating to his particular sample of female patients between 20 and 25 who took two to eight months to become pregnant, with an average of four months.

additional children and are unlikely to be willing to leave it up to chance. Hutchinson and Szilard believe, however, that a method of birth control which appreciably reduces the chances but does not rule out the possibility of pregnancy, is not without merit and might perhaps be favored in areas where religious attitudes are opposed to the divorcement of sexual intercourse from the purpose of procreation.

There seems to be no need at this time to resolve the existing divergence of opinion relating to acceptability, since no developmental program is called for in any case.

Lead # 19. Cauterization of the Uterus.

Cauterization of the entrance of the tube into the uterus may serve the same purpose as ligation of the tubes. This will prevent the entrance of the ovum into the uterus from the tube just as well as ligation of the tube, and has the advantage of avoiding abdominal surgery. Dr. Mortimer Hyams of New York fills the uterus with a radio-opaque substance and cauterizes on the x-ray table.

Dr. Howard Taylor believes that gynecologists might have been remiss in not giving this possibility more attention. Dr. Folsome has misgivings about the method but thinks that further engineering development might improve it. Dr. Gamble told us that there is some interest in this procedure in Japan.

Before making any recommendation it would be necessary to make further inquiries, including having a conference with Dr. Hyams.

Lead # 20. Sterilization of the Ovaries by X-rays.

If it were possible to stop ovulation for good without causing symptoms of castration by giving a small dose of x-rays to both ovaries, this procedure would be preferable to ligation of the tubes.

It is doubtful that temporary sterilization with x-ray ought to be recommended because of the genetic changes produced by x-ray.

Before making any recommendation for further research, it will be necessary to inquire whether there is a sufficiently wide margin between the dose that will stop ovulation for good and the dose that will lead to symptoms of castration.

In order to make further inquiries on the subject, it is planned to take up the matter with Dr. Ira Kaplan of New York and Dr. Robert Hotchkiss of the Cornell Medical Center and Dr. Cantril at the Tumor Clinic of the Swedish Hospital in Seattle, Washington.

We are in no position to make any recommendation at this time.

Lead # 21. Permanent Sterilization of the Male by Means of X-ray.

Permanent sterilization of the male by means of x-ray raises the same questions as does permanent sterilization of the female.

In addition, the general question of acceptability of permanent sterilization of the male is involved and will have to be examined. (See Lead # 15 on Vasectomy).

No recommendation for further research can be arrived at until the inquiry indicated in the preceding paragraph has been completed.

Lead # 22. Suppression of the Pituitary Gonadotropic Hormones by Antibodies (Antihormones).

Some simple facts in this field appear to be well-established. For instance it seems quite clear that pituitary gonadotropic hormones of the pig may be injected into the rabbit to immunize the rabbit against the pig hormones. The rabbit's antiserum, when injected into the pig, may suppress the pig's pituitary gonadotropic hormones, but such passive immunization is transitory and requires frequent repeated injections for its maintenance. Therefore it is not practical for our purposes.

However, a number of phenomena falling in this general field have been described for which there is no clear interpretation and therefore the possibility of more durable suppression of the pituitary gonadotropic hormones should not be entirely ruled out at this time. Seeger Jones mentioned that if a practical method of suppression of the pituitary gonadotropic hormones in the female were possible, the suppression of the luteinizing hormone or the luteotropic hormone would appear desirable rather than suppression of the follicle stimulating hormone.

A survey of the literature and further discussions with Roy Hertz and others might supply the answer to a number of pertinent questions that might be raised. Szilard is inclined to believe, however, that further work using modern immunological methods may be necessary to clarify the issue to the point where one can either definitely reject this approach or clearly see how it might be useful for our purposes.

No clear research program can be outlined at this moment.

Lead # 23. Preventing Spermatogenesis by the Feeding of Arginine Analogues.

Men fed a diet free from arginine will within a short period of time stop producing sperm. If an arginine analogue could be found which is not immediately decomposed in or eliminated from the body, by feeding such an arginine analogue one might maintain a certain level of it in the body and might conceivably interfere with spermatogenesis without interfering with protein synthesis in general. An inquiry may be made into this possibility by examining how other known amino acid analogues behave in the body.

Pending such an inquiry, the way is as yet not open to program research along this line.

Lead # 24. Fertility Control Based on Spermicides or Oocides.

The question may be raised whether certain drugs may not be secreted into the genital tract of the female and kill the eggs before they reach the uterus or affect the sperm and thereby prevent fertilization of the egg. Thinking along these lines is impeded by our lack of knowledge concerning the secretion into the genital tract of the female and the resorption from the genital tract of the female into the body. For instance, Reynolds has asked whether spermicides like the yellow pigment described by Roy Hertz, which proved to be spermicidal in vitro, might be locally applied and might remain in the genital tract for a week or ten days or whether they would be quickly resorbed. Can certain spermicidal agents be taken orally by the female and secreted into the genital tract? (Reynolds) Szilard has asked whether a high-titer antibody against sperm might be introduced into the genital tract which might remain active there over a long period of time without being resorbed and without sensitizing the female against foreign protein. Furthermore, there is the question as to whether progesterone

could not be efficiently administered to women in the form of vaginal suppositories, relying on the resorption of progesterone from the vagina.

In view of all these possibilities a research program ought to be set up to learn something both about the secretion of simple chemical compounds and antibodies into the genital tract and the resorption of them from the genital tract.

Lead # 25. Control Based on Affecting the Cervical Mucus.

The cervical mucus which is secreted is very viscous during most of the menstrual month (Stone) but just about the time of ovulation the viscosity drops very low. It might be that the spermatozoa could not get through the cervical canal if the viscosity of the cervical mucus remains high at the time of ovulation. Very little is known about this secretion and experiments designed to test how it could be influenced by medication would appear to be worthwhile.

No recommendations concerning specific program research are made at this time, pending further inquiry into the question.

PROCEEDINGS

Tuesday, September 2

In Attendance: Kingsley Davis, Paul S. Henshaw, Frederick L. Hisaw, William I. Lourie, Robert G. Snider

## Factors Causing Lag in Fertility Control Development

The question was raised as to why scientific development in the field of fertility control has been slower than in other fields of biology. Even in situations which seem to call for further research, when in other words the situation is ripe for work on fertility control, the work has not been pushed along. For instance, there has been considerable research on aminopterin, which is an antagonist of all the estrogens; but it has not been investigated from the standpoint of fertility control in human beings. It was brought out that in one case an investigator had prepared a paper on the fact that administration of aminopterin produces abortion in laboratory animals. His superior did not allow him to present this paper because he (the superior) was interested in possibly using aminopterin for cancer therapy and was afraid if the news got out that it caused abortion it would never be considered for his purpose. This case illustrates that research funds and interest have been primarily directed toward other ends than fertility control.

The reason for the lack of funds and interest is in part due to the lack of an organized effort, but behind this is the fact that in our culture everybody knows that contraceptives can be obtained from a drugstore. It is taken as an accomplished fact, not necessarily requiring a physician who is for the purpose of treating illness. The demand upon the physician is for help in overcoming sterility, dysmenorrhea, irregularity, impotency, etc.

The physician accordingly takes more interest in using the knowledge of reproduction for treatment of these illnesses than for the control of fertility. He sees nothing challenging on the birth control side. This fact is illustrated by the situation at the Margaret Sanger Clinic. There they find it easier to staff their anti-sterility clinic than to staff their family-limitation service. The doctors in the anti-sterility clinic feel a certain challenge in the work, and a degree of prestige. They therefore furnish their services free of charge. The doctors on the birth control side feel that the work is mechanical, and they have to be paid for their services.

Because of the direction of demand, the pharmaceutical houses have also tended to neglect the development of new birth control techniques in favor of products for overcoming sterility and other reproductive disorders. It was mentioned, for instance, that two companies were once actively engaged in research on lithospermum, but dropped it. A scientist with one of the two companies mentioned that the reason was this: The problem was a difficult one; there was no encouragement in the general field; and the company felt there was greater commercial opportunity in developing products to overcome sterility.

Without doubt a part of the difficulty has been the general prejudice against birth control as a subject of scientific interest. As one participant put it, we in this group are sinful plotters in the eyes of certain powerful groups. The restrictions on discussion of birth control and diffusion of birth control information are well known. But things are changing, and the history of research on sex is enlightening. Over 20 years ago Yerkes and others established a committee for the study of sex. It began first on the physiology of the subject, although it was interested in psychological aspects as well. This committee had quite an impact. It gave people working in the field a decisive stimulus and resulted in substantial research contributions. Its success shows not only that it is possible to do scientific work on tabooed topics but that one of the means of getting such work done is to

have a nuclear group who are interested, who integrate the field, and who find funds for and give encouragement to individual scientific workers. At present there is nothing in the field of fertility control that corresponds to such a coordinating scientific body. The thought was expressed several times that research workers need not only funds but also a pat on the back for their work, and means of associating with other workers in tho same area and finding out about their results.

From the standpoint of scientific development, it would appear foolish to get drawn into controversy over birth control. Argumentation would have little effect. Probably the best way of solving the situation in which official pressure is brought against fertility control would be scientific development itself, for this might allow some of the controversial points to disappear from the scene. It should be borne in mind that in a sense pressure groups in the United States can afford to be prejudiced against birth control because this country has no critical population problem. In the heavily settled agricultural areas of the world, on the other hand, the necessity of birth control is so apparent, and it is so little used today, that the authorities are forced to be receptive to the idea. It is these areas that may prove the immediate users of new techniques of fertility control.

## An Institute versus Grants-in-Aid

In admitting the necessity of some kind of organized developmental program to overcome the lag previously noted, the question was raised as to the type of organized effort that would be most efficient. At the cheapest and simplest level, it was pointed out, would be a sort of strategy board for general planning and the administration of grants-in-aid. When done well, this sort of effort can be quite successful on small funds. Dr. Hisaw cited for example the committee on sex research and endocrine secretions, of which Dr. Corner

has been chairman. This committee never had more than approximately $75,000 per year, yet it got a great deal of research for this amount. The reason is that such a program can provide just the extra means needed to get certain things done in established laboratories and universities. These institutions have the personnel, the equipment; it does not take much extra to get specific work done. The same laboratory animals can generally be used on a variety of projects. The same is true of the equipment and personnel. The cost of any one project is therefore partly supported by funds coming in for other work at the same time. On this basis too, government funds would probably be available.

Perhaps the next step in complexity of developmental organization is the establishment of a coordinating and information center. The Cornell center on corn genetics was mentioned as an illustration. Such a center serves as a repository of knowledge in a given field, as an information and exchange center enabling investigators to be posted on latest developments, and as a means of avoiding needless duplication and a stimulus to getting results tested and checked. Such a center can function with a small staff. It can promote an annual meeting of specialists in the field, where personal contact aids the exchange of scientific information. It can also serve as a center for publishing in the field, getting out either a journal or a monograph series. Finally, such a center helps in the international exchange of information and personnel.

Neither of the two organizational forms mentioned involves the expense of separate laboratory facilities and a staff devoted to fertility control alone. However, the third possible type of organization -- the separate institute for research in physiological reproductive control -- does imply an entirely separate set-up, with the expense for all the overhead being borne by funds for the support of fertility control. It was Dr. Hisaw's

opinion that at least 50 per cent of the research conducted in such an institute could be carried out elsewhere at an established institution, with no loss in quality. It would be pure research which any good laboratory could do. Any specific problem requires research that turns out to be applicable to other problems as well, as the cancer laboratories illustrate. A limited or specialized objective for a research institute means possibly an uneconomic use of facilities. In addition, such an institute might find it more difficult to obtain government funds than would a research organization having other purposes as well. It might have the disadvantage of drawing opposition to itself by virtue of its specialization on fertility control, whereas work of this type is dispersed as an apparent part of other work in a more generalized laboratory.

The institute idea, however, can be defended. Granted sufficient funds to support it, it can perform other functions in addition to research. It can serve as a coordinating and information center. It can produce publications in the field of its interest. It represents a tangible evidence of organized research in the field of fertility control, thus stressing the importance of this work and serving as a basis for requesting research funds. It would offer a career to young scientists devoting themselves to fertility control. It could also devote itself to strategic types of research difficult to get done in established centers.

This discussion of differing organizational measures was not, however, a discussion of mutually opposed alternatives. It was rather a consideration of degrees of concentration of funds and personnel. The point was made that an overall strategy board would be needed regardless of whether or not there was an institute. Also grants-in-aid would be necessary in any case. Consequently, the question of whether or not a separate institute is recommended depends partly on the funds that would become available. If enough support

were obtainable to have the indispensable things as well as an institute, then the question would be cast somewhat in the form of marginal utility.

One objection to an institute is that it would take some time to get it under way. Dr. Henshaw stressed the emergency with which we are faced. The program should not be held up while we are waiting for an institute, whatever may be the merits of the latter at a time of no emergency.

In the discussion of the possible functions of an institute, the question of clinical testing arose. This is one of the more delicate of the tasks to be accomplished. It was pointed out that there are really four steps in testing, as follows:

(1) Laboratory testing with animals.

(2) Clinical testing with human subjects, carefully designed and thoroughly supervised.

(3) Clinical testing with a wider human group, less carefully studied.

(4) Community or field testing on the general population.

Step number (2) might present certain problems for a separate institute. It would have to have hospital facilities, which might be difficult to obtain. It might not find it easy to obtain typical subjects, because they would not arise out of routine work but would have to be brought in for this purpose. For a wider group -- i.e., involved in steps (3) and (4) -- an institute might send out teams, train the investigators, etc. When all is said and done, a great deal of the clinical testing that would have to be done could be done in already existing facilities, under a grant-in-aid program. The place in which a product is tested depends in part upon the nature of the product. If the product is one which presumably gains its effect by preventing ovulation, this can be tested in almost any clinic, and it would probably require little financial aid, being possibly a by-product of other research. If, on the other hand, it is one preventing implantation of the fertilized ovum, special facilities and conditions will be required.

## The Planned Parenthood Program and Its Relation to Our Work

Dr. Henshaw gave a brief account of the interest in the Planned Parenthood Federation in the development of research on physiological methods of fertility control. He pointed out that his organization has just prepared a document detailing 22 approaches to the problem, copies of which will be made available to our group. This document was prepared for the meeting sponsored by them at Arden House on September 13-14, at which about 30 specialists will be present.

He said that he considers five approaches to be the most promising, as follows:

(1) Hormone and enzyme research, including the anti-hormones and anti-enzymes. This is perhaps the most promising field. It represents a broad category of activity, since there are many aspects to it, all of them interrelated.

(2) Immunological research, including work on spermatoxins.

(3) Symbiotic organisms, such as bacteria or yeast in the uterus.

(4) Fluid physiology, such as applies to mucous, semen, and contents of the tubes.

(5) Dietary approach.

Dr. Henshaw also summarized the projects in the physiology of reproduction which the Planned Parenthood Federation has under way. These are grants-in-aid studies. The program is as yet small in scope when compared with the total volume of research in biology.

These activities raise the question of the relationship between the Federation and the Conservation Foundation with respect to their efforts in a common field. Agreement was reached that every effort must be made to avoid needless overlapping. Although the two organizations have not worked out any complete plan of integration to begin with, they have been in touch

with each other all along. It was felt that as the work progresses the relationship can be worked out successfully. This is made possible particularly by the fact that the roles of the two organizations are different. Mr. Snider pointed out that the Conservation Foundation is not an operating agency. It prefers to play the role of a catalyst. With reference to the present work, it is merely sponsoring the working out of a blueprint for a program of scientific development and the initiation of the first steps to get it underway. The Foundation is not interested in operating the program once it is initiated. The Planned Parenthood Federation, on the other hand, is an operating agency which will necessarily have a continuing interest in this field. The Federation also has an interest in promoting the use of adequate birth control methods, and consequently in the testing and diffusion of such methods.

Cooperation with Commercial Firms

At present there are no representatives of commercial pharmaceutical firms associated with this project. The only reason for this lack of representation is to guarantee that the Foundation is not party to formation of any vested interests in the field of chemical compounds with fertility control possibilities. However, all recognize the need for more cooperation with commercial firms for research, supply and testing of a cheap effective product. Much, however, will depend upon the nature of the products recommended as a result of the investigation. Research on some chemical compounds such as sterols is best done by such firms. Something easy to make will readily be made available to physicians by the industry. Other products, more difficult to make, will find companies disinclined to risk production. In some cases in which many by-products result from a procedure aimed at one specific chemical, the producing company may have a whole program on

its hands. In addition, as mentioned before, contact with commercial firms is necessary to induce experimentation in directions where no effort would be invested without such encouragement.

Means of instituting coordinated contact with the industry were discussed. One suggestion was to explore the possibilities of working through a trade association which might be persuaded to set up a committee to represent the industry for a contact, clearing-house function with this program. Mr. Snider said that he would consult Mr. Merck concerning this possibility.

Patents and their importance to a future program were discussed. Dr. Henshaw stated that till recently the emphasis had been upon trying to find ideas and that patent implications were just now being realized. The Planned Parenthood Federation has had to develop a formal patent understanding with any companies providing it with test material. Copies of this patent stipulation will be brought to the committee sessions. Dr. Hisaw pointed out that the willingness to defend a patent, a costly undertaking, is crucial in this matter. In view of the possibly tremendous market for products for fertility control and of the necessity of keeping the cost to the user to a minimum, the matter of patents may be investigated more thoroughly in future sessions.

PROCEEDINGS

Wednesday, September 3, 1952

In Attendance: Kingsley Davis, Clair Folsome, Paul S. Henshaw, Frederick L. Hisaw, William I. Lourie, Robert G. Snider, Leo Szilard

Target Considerations

Since the report will go to people with little social science background,

it was admitted by Dr. Davis that it might be necessary to spell out in detail the social cultural problems of such a program, not only for the donors, but also for technical people.

This statement raised the question as to whether the target should be specified in terms of social conditions as limiting factors on the use of certain birth control methods. For instance, as Dr. Henshaw said, it was not enough to carry on research and find safe products, but that we would be limiting our objectives too much if we did not also consider utilization of such products. Dr. Davis stated that the present program was a limited program restricted to finding only the best methods and that the target of this immediate program should therefore be strictly limited.

After this step has been passed, social conditions will be explicitly stated for utilization of such methods.

Lourie asked if it were worthwhile to define the target as aimed at limiting the total number of family rather than at child spacing, that estimates indicated a significant reduction in the birth rate if women stopped having children after six pregnancies.

## Sterilization

Dr. Davis then brought up the question of sterilization and suggested it should be considered in our report for the sake of completeness, and because of its accepted use in some places. Sterilization is a good, safe method in civilized communities, and it is the preferred method of birth control in Puerto Rico.

According to Dr. Henshaw, in the United States in some places, the medical profession practices ligature of the tubes after the eighth child. The figure eight is an arbitrary one, and the medical profession would probably be hurt if they were challenged on a legal basis. However, eight

is a high enough figure to be reasonably safe, and so far they have not been challenged. But, he raised the question of public policy in case the figure should be lowered. Dr. Davis thought three or four was the accepted minimum in Puerto Rico.

Dr. Henshaw also mentioned the possibility of using a new technique of scarifying by cautery as a painless, quick, cheap method of sterilization.

Dr. Hisaw raised the question of sterilization of males. The discussion brought out the fact that although male potency has a high value in most societies, that actually, in certain parts of Puerto Rico, some doctors had large practices devoted to male sterilization.

In regard to the original question, Mr. Snider stated that the idea of limiting families after a set number of pregnancies was probably more satisfactory from a demographic standpoint than any other, because it did not cut out a whole age class.

## Lag Factors

Dr. Hisaw mentioned the tremendous number of scientific publications on Cortizone in the last few years, and that Merck has a full-time librarian keeping track of them. Dr. Davis was interested in this as a means of showing how relatively small was the amount of the attention given to fertility control as measured by the number of articles or pages devoted to both subjects.

## Ovulation as a Point of Attack

It is difficult to summarize the highly technical and rewarding discussion led by Dr. Hisaw but the main points appear to be the following:

In primates during advanced pregnancy the ovaries become inactive and the placenta takes over. Ovulation does not occur and mature follicles do not develop. If we knew why we could figure out how to regulate ovulation.

We have, however, learned from laboratory studies of several species including monkeys, that a follicle is a delicate organ and that to bring it to experimental ovulation is an extremely difficult job. If the follicle is a little young or a bit cystic there will be no ovulation in response to gonadotropins. The delicate balance in precise conditions apparently necessary for ovulation make ovulation a possibility to control.

Secondly, we know the ovum probably has the shortest life of any cell in the body with possible exception of the erythrocyte. A growing follicle either terminates in ovulation or the ovum becomes atretic and dies. It does not persist in a dormant state for an extended period. The great majority become atretic. It is important to find the time at which the follicle is most susceptible to experimental influences.

From the other point of view, ovulation does not have to occur to have a normal menstrual cycle. As Dr. Folsome indicated, generally the older women are the more frequent in anovulation. He said you could expect two anovulatory periods for the average thirteen cycles per year for any woman. Both he and Dr. Hisaw agreed that anovulation is more frequent than people think. Thus, the problem is to defeat ovulation without interference with the menstrual cycle.

Other possibilities, such as preventing implantation, early abortion, seemed much less desirable to Dr. Hisaw than the prevention of ovulation. The other methods have more complicated physiological, psychological and social repercussions.

Now, if we could regulate ovulation, what is the next step? Something to administer with a specificity for reproductive processes and no side effects. If we could administer such a product by mouth it would be good. However, the question of when to administer the product is somewhat troublesome since it is still difficult to tell for humans the precise time of ovulation.

Dr. Folsome stated that women approaching a premenopausal condition had a high degree of anovulation which presents much hyperplasia and aberrant conditions to the gynecologist accompanied by poly or secondary menorrhea. His main point was that in this condition, although there is some bleeding, the patients do not flood. If this condition could be simulated it would be a fine method.

In regard to bleeding, Dr. Hisaw indicated that after estrogen, progesterone, or estrogen plus progesterone therapy, regardless of the thickness of the endometrium, bleeding always occurred when the supporting stimulus furnished by the hormones was withdrawn.

Dr. Hisaw discussed what might be called a new concept of the estrogen, estriol. He said that in pregnancy in the human being there are three estrogens secreted by the placenta. The placenta becomes an autonomous structure and, judging from experiments on monkeys, the placenta is capable of continuing its endocrine function in the absence of ovaries, fetus, and pituitary. Estradiol, estrone, and estriol are found in the placenta in proportion of approximately 1:1:27 by weight respectively. However, in regard to activity estradiol is the most active; estrone is 10 times less effective than estradiol; and estriol 200 times less effective than estradiol in promoting uterine growth in castrated rats. In the metabolic processes of the body estradiol is degraded to estrone and the reaction is reversible, but once either hormone is converted to estriol, the process is irreversible.

After citing much evidence, he stated that the biochemist had led us wrong by considering estriol only as a degradation product of estradiol and estrone. It seems quite probable that it is secreted as such by the placenta and there is reason to think of it as a true hormone of pregnancy. Its function appears to be that of a buffering action on the more active estrogens. Since estriol gives very few side effects, and in general has weak activity,

it would lead to possibilities for control. He outlined a procedure for finding the dosage in monkeys, for instance, for the amount of estriol needed to control ovulation.

At this point, Dr. Davis attempted to extract from Drs. Hisaw and Folsome an estimate of the amount of time necessary to determine whether estriol would be of effect as a method of control. With allowances of leaving time to get latent effects and repeat experiments and the like, Dr. Folsome said it would take from three to five years and Dr. Hisaw agreed with him.

Dr. Hisaw also mentioned the pregnane series and mentioned that as yet little work had taken place in this field. Of the eight possible isomers of pregnandiol only two have been tested in the laboratory. He mentioned the problem of insolubility as a stumbling block in this field, and as providing for difference in results obtained by different workers.

It was interesting that Dr. Hisaw summed up the discussion in the following way. He said the emphasis until now had been -- can you make a monkey ovulate? Now the question is -- can you keep a monkey from ovulating? Such change in emphasis may have world-wide effect.

During the discussion Dr. Hisaw mentioned many of the interrelationships of the endocrine system to those less informed members of the working group and answered their questions concerning other possible hormonal methods of control. For example, in answer to a question of Dr. Henshaw's regarding the corona, and anti-hyaluronidase as a means of preventing fertilization, Dr. Hisaw stated that since fertilization took place almost instantaneously that any such agent as an anti-hyaluronidase would have to be present in the genital track right at the time of attempted fertilization. He also stated that since this was a cytologic process that such agents would likely have side effects. He also answered several questions by Dr. Szilard concerning possible delay of the first menstruation by use of long continued doses of progesterone by pointing out the physiologic changes likely to occur and the probable lack of social acceptance of such a method.

PROCEEDINGS

Thursday, September 4, a.m.

In Attendance: Caryl Haskins, Frederick L. Hisaw, Paul S. Henshaw, Evelyn Hutchinson, William I. Lourie, Robert G. Snider, Leo Szilard, Kingsley Davis

## Suggestions Deriving from the Experience of the Committee on Sensory Devices

The session began with a request that Dr. Haskins comment on the experience of the Committee on Sensory Devices set up by the OSRD. It was felt that the experience of this committee would serve by analogy to show how some of the things might be incorporated into our program. The Committee was formed to suggest leads in research for the development of prosthetic aids for people with sight and hearing disabilities. It had small funds, somewhere on the order of $100,000.

The Committee proceeded by appointing a central laboratory to undertake the job of investigating the literature and for making recommendations on project leads. After a year of this, seven or eight research contracts were placed. As it turned out, the possibilities proved to be fairly limited. The Committee is still in existence, but the central laboratory work has been discontinued.

By analogy, it was suggested that our group might set up a central committee, and possibly appoint a laboratory to serve the same function as was done in the case of the Committee on Sensory Devices.

Such a laboratory might be located in a university. It was pointed out, however, that in the one case the goal was a universally accepted one, whereas in our case it is not. Therefore there might be some difficulty in locating a central laboratory at a university. It was also pointed out

that for our purposes it is probably best not to be connected with government organizations, although the use of government funds would be advisable if it proved possible to work out an arrangement to get them. Dr. Hutchinson commented that more field experiments should be done in foreign countries whenever possible, and also as much of the laboratory research as possible. The opinion was expressed that under these conditions foreign countries might take more pride in the products developed, and that the work would be less subject to adverse propaganda. Preferably, as many of the research staff as possible in foreign areas should be of local origin.

The thought was suggested that an Indian university might well do laboratory research of the type needed, possibly with funds from UNESCO. At the same time it was pointed out that UNESCO is subject to intensive pressures, that connection with such a large organization would probably slow down the program. This suggests that the best source of support would probably be a private foundation, especially one with wide interests in foreign areas. The point was stressed that the American personnel sent into foreign areas for scientific research should be of the very best type. Otherwise, the entire program in these countries might be irreparably damaged.

## The Question of a Separate Institute Again

The Committee on Sensory Devices did not undertake to set up a separate institute or laboratory for its work. It merely appointed for an interim period an established laboratory to do some of its work for it. This fact raised once more the question of whether in our program it is desirable to think in terms of a separate laboratory or institute set up for our specific purposes.

It was pointed out that such an institute would serve the same survey function as was done by the laboratory in the other case. This is a highly

necessary function, especially in a broad and inchoate field where careful work must be done before one is able to think in terms of specific projects. A second function for such an institute would be the performance of pilot experiments. It was pointed out by Dr. Haskins that it is inadvisable to make contracts for research most of which will turn out to be fruitless. Pilot experiments can throw light on the feasibility of a project at far less cost. Once the literature survey and pilot experimentation have been done (and these can be done in part simultaneously), this contract can be farmed out to established research agencies.

Dr. Szilard made the point that in a field such as that of the physiology of fertility control, fresh talent will have to be brought in. By reason of the neglect of the field so far, there is not much existing talent to draw on. With a separate institute, it would probably be easier to get good young men, for they could be employed directly, rather than having to sell them first to a university. Yet Dr. Hisaw saw certain difficulties in staffing a separate institute. It was mentioned, however, that it could be done with leaves of absence -- in fact, some universities in financial straits would welcome leaves of absence for members of the faculty. So far as a separate institute is concerned, the difficulty is really with the director and top personnel. Young men can't expect tenure in any case so that work with an institute, the life of which was limited, would not necessarily be a blind alley to them. Yet one advantage of establishing a research unit or laboratory within a university, would be that research associates can then be appointed with the possibility of such people taking their Ph.D.'s in the university concerned at the same time as they do their research. Dr. Hisaw suggested that the best men, being in such great demand, might turn down an opportunity at a small research institute with a limited existence, so that second-rate men would be secured. Again, however, it was mentioned

that the director would be a crucial factor. He should be a man who can inspire and carry weight with younger men. In that way he would overcome many of the staffing problems such as a separate institute might have.

Dr. Haskins pointed out that three things were really needed: (1) advisors in various fields to form a sort of advisory or administrative committee; (2) fresh talent specializing in particular areas of work being developed; and (3) research projects to get discoveries made. Everyone agreed that it is quite dangerous to make projects too early in the game. First, a good grasp of what is possible and feasible must be obtained. The three things needed are obtainable without a separate institute, although, as mentioned earlier, some of the necessary functions could be performed by an institute. It was universally agreed that in the early stages, focussing is needed, and that a nuclear group should be set up, composed of people with a strong interest in the purpose of the project. It was also agreed that a small organization and a small group would be better than a large one, especially in the early stages.

The point was made that the field of physiologic fertility control has not yet been adequately surveyed. Such a survey will require more time than has yet been possible to devote to it. If a nuclear group devotes itself to getting this done, it is probable that a good many more leads would be turned up, for instance a letter written to the University of Witwatersrand where a group is interested in native pharmacopeia, would turn up some information on herbs and drugs that affect reproductive capacity in one way or another.

Another point mentioned in connection with the question of staffing a separate institute or laboratory was that there would be certain facilities lacking, which are ordinarily counted on. An adequate general library would not be available -- even music and other amenities might prove less available

than in a university community.

The desirability of a separate institute hinges comewhat on the adequacy of funds. It is not a case of an institute or something else, unless the funds are limited so as to force such an alternative. It was completely agreed by the discussants that at the very minimum a coordination center and clearing house would be required.

It was also agreed that five years is a very short time for a research organization to produce results. It takes a year or two to get started and another year to wind up under these conditions, so that the portion of the time used most fruitfully is very limited. It was suggested therefore that in our project we should aim at at least ten years, but hope to secure the funds for the first five. More funds would probably become available later on.

## The Lithospermum as a Lead

Dr. Haskins, whose laboratory has worked on this compound, started off by saying they had, from their standpoint, become discouraged, and that he would not recommend Lithospermum as one of the better prospects. The reason is that it is unstable and its concentration is low, so that a great amount of material has to be handled to get a reasonable amount. The material actually comes in as hay. The impression that other laboratories working on it have is much the same.

However, it is established that Lithospermum will prevent ovulation. The question of side effects was raised, but Dr. Haskins suggested that Dr. Zahl in his laboratory would know the details on that better than he. American Indians used it in tea as a means of fertility control, but the literature on such use by Indians is scarce. The US Department of Agriculture has a report containing one paragraph referring to this matter. No one could say where information could be obtained as to just what the Indians did.

The Human Relations Area Files at Yale have been doing research with no results on the matter.

Dr. Zahl's interest in Lithospermum did not come from the standpoint of controlling fertility, but rather from the standpoint of cancer research. He was interested in separating mammary development from ovulation and hence in controlling ovulation. He was working with rats and he found that lithospermum was quite practical to do what he wanted it to do.

Dr. Henshaw volunteered the information that Dr. Noble at the University of Western Ontario has perhaps gone a bit further with work on lithospermum. He, along with Dr. Zahl, will be at the Planned Parenthood Federation meeting on September 12-13, where it is expected that he will give a full report on his findings. The substance has been used considerably, but apparently no one has succeeded in purifying it completely, yet if it were used in Burma or some other remote part of the world, it would be of great advantage, as Dr. Hutchins/pointed out, to have it in crystalline form. Admittedly, it could be used in an unpurified form for human subjects and its usefulness for human subjects could be ascertained.

Dr. Hutchinson raised the question as to whether any taxonomic botanist has looked into its family tree. Dr. Haskins knew of no such thorough survey. Two or more related species have been looked into with negative results. However, there is a large number of species some of which are used as ornamental plants. DeLazlo in England, according to Dr. Henshaw, has over 100 oral contraceptives on the list that he is compiling. He has been quite diligent in turning up all results on oral contraceptives. It is expected that he will be publishing some of his findings soon.

It was pointed out that there are many reports of sterility resulting from the handling of specific substances. It has been reported that in Mexico, the natives put a substance in the water of ponds to paralyze or

kill fish. They eat the fish but do not drink the water. The cattle, however, drink the water and the cattle raisers complain about the practice because it makes their cattle sterile. Dr. Tislow knows something about this, and he will be at the Planned Parenthood conference.

Dr. Hisaw raised the question of whether lithospermum will do anything that some of the hormones will not do. The hormones as yet are better known.

It was agreed by everyone that lithospermum represents a sufficiently promising and interesting lead to deserve to have further research done on it. It was pointed out by two or more participants that the side effects do not seem to be necessarily detrimental or permanent. Yet, despite the promise, very little research has been done on lithospermum from the point of view of controlling fertility. For instance, no primate research has been done yet. Lithospermum would therefore have a fairly high priority in any research program. So far, it apparently has not been used on males, so that the effects on males are not known.

## Males versus Females

The question arose as to whether our group should rule out possibilities of research on means of suppressing fertility in the male. The fear was then expressed that if married men had their fertility inhibited, unmarried men might derive a certain prestige from not having this done to them. On the other hand, men in our culture have sometimes been alleged to derive a certain advantage from sexual competition because the danger of pregnancy was not present. The fear was also expressed that family problems will arise from the fact that husbands made infertile would detect marital infidelity in cases in which it would otherwise be undetected. The upshot of the discussion was that this is a matter that can't be decided *a priori* for all cultures. In fact, we should have to think in terms of the possibility that

different procedures and products will be usable in different cultural situations.

One objection to research on male fertility inhibition was that spermatogenesis is a continuous process. It therefore may require more of a physiological effort to suppress. On the other hand, it was mentioned that something permanent and regular might be all right. The cyclical character of the woman's reproductive functioning is such that counting and varying treatment at different times are needed in the case of some methods.

It was pointed out that testosterone would suppress testicular activity in males if given in very large doses.

## Miscellaneous Notes

It was agreed that the dietary approach, while one worth investigating, is less promising than the hormone approach. Insofar as the dietary approach is helpful, it may turn out to be connected with the hormone approach.

It was agreed that possible leads should not be ruled out always because of their dangerous or toxic qualities. It may prove possible to refine materials in such a way as to eliminate toxic qualities, in any case, the experimentation will be done on animals first. In this connection, it was pointed out that aminopterin in microgram doses would cause monkeys to lose weight, experience blood changes, and die from folic acid deficiency.

Any method causing abortion should be excluded from the list of promising leads in countries where there is the serious risk of opposition involved.

In the development under consideration, the great obstacle is side effects. A great many products will suppress ovulation or prevent fertilization, but the undesirable consequences restrain the use of these materials.

(Afternoon Session)

Liaison with Commercial Firms

The question came up of how a program of scientific development of the sort contemplated can best cooperate with and derive advantage from research in commercial firms. It was pointed out that at present the vaginal tablets have been reduced in cost to a fraction of a cent each. Dr. Folsome pointed out that from a commercial point of view, the disintegration time of a vaginal tablet was crucial and that anything that requires 30 seconds or more for disintegration was not feasible. Hence, the filler is important. Aluminum subchloride mixed with potato starch can form a tablet which costs only 1/100 of a cent to manufacture. Of course, from a competitive point of view, the price may be much higher.

It was suggested that one of the things that should be done in our group's program was market research on the business advantages of low-price products.

Dr. Folsome said that if a program is inaugurated, with high-ranking scientists in charge, more interest will be stimulated. There will be more papers published, more of the knowledge will be in the public domain and less confined to research laboratories where there is vested interest in restricting the information. Yet at the same time, the manufacture of products requires commercial enterprise, and above all require pilot plants. In the case of work on Vitamin A, there were approximately eight teams of researchers in the field at one time. They were using different processes. The industry wisely decided to get together and to pool research findings. This is the sort of thing that might be done in the field of fertility control.

The possibility of manufacturing plants in foreign countries is already a reality. Ortho is putting up a plant in India to manufacture perceptin.

They intend to use Indian materials as far as possible. The price will be high at first, but may be reduced later on. The possibility of using WHO as distributing agency was discussed. It seems more likely, however, that the pressure would be too great and that a more favorable possibility would be that of having the governments or the Public Health Departments of particular nations take over distribution.

The Ortho Foundation has furnished clinics in Puerto Rico with contraceptive products. Unfortunately nothing has been published as to the results, although the material has been and is in the files of the company, which would furnish the basis for publication. In fact, some of this material has now become available for publication because of its protection by patents.

It is desirable to get the more established business firms to thinking in terms of world problems. It might also be realized that, if governments take over the purchase and distribution, the manufacturing contract becomes a matter of cost-plus. This form of distribution would alter the competitive set-up somewhat and the pricing system from the standpoint of private companies. If industry can be induced to see the problem from a long-range point of view, it will doubtless realize the advantage of supporting basic research, together with the licensing system. It might take the form of the Wisconsin set-up in the field of vitamins. This arrangement lasted for 17 years but, as Dr. Hisaw said, the companies were willing to continue after the Supreme Court decided adversely. They wished to have the University test their products and certify them as it had been doing.

The Planned Parenthood Federation has a patent agreement which it took over largely from the National Research Council Committee and which it is now in the process of revising. It was mentioned that the Merck Company agreement with Professor Waksman at Rutgers was the type of arrangement that worked satisfactorily to the profit of both the company and the university.

## Methods Indicated in the Human Fertility Colloquium Material

Dr. Henshaw presented a general introduction to the brochure concerning possible methods of fertility control which will be discussed in detail at the Colloquium on Human Fertility September 13-14. After this introduction, there was a short discussion upon the problem of presenting methods of control in general.

To some of those here assembled it seemed most logical to consider methods of control according to the point of attack in the physiology of the reproductive system. For each point of attack, methods could be listed according to which seemed the most feasible. A listing by point of attack would also indicate areas where possible points of attack existed but no methods as yet were known. It was pointed out, however, by members of the group that this type of methodology would not provide for classification of dangerous side effects of particular methods. That to do this, a detailed listing of each method was necessary. It seemed likely that both methods would have to be used.

At Dr. Szilard's suggestion, the methods in the Colloquium material were taken up in reverse order.

### 22. Symbiotic Organisms

According to Dr. Henshaw, there has been some work done in this field. For example, there is a paper based upon the cases of 153 sterile women with bacterial flora of some anti-sperm action in their vaginal tracts. Since cervical mucus is an excellent culture medium, the women have probably had this for many years. It was pointed out that 133 of these cases had the same type of organism -- a pleuro-pneumonic type. The E. coli group of organisms was also indicated as of possible effect. Dr. Folsome said this

whole method could be tested very rapidly on human patients in some gynological clinics with great chance of early success in proving whether the method is effective or not. However, he stated he would like to see mass culture of such organisms for further details. Dr. Hisaw indicated that it took much courage, he thought, to transfer some bacterial flora from one woman's vaginal tract to that of another.

It was decided to get Dr. Seeger-Jones to speak to us when she comes from the conference.

Dr. Folsome mentioned that 99% of the bacteria of the vaginal track have never been identified. He also stated that in the realm of symbiotic organisms that if yeasts were considered he would be fearful of their use in a control program.

21. Wharton's Jelly

The committee was presented with conflicting reports concerning this substance and its efficacy. It was decided to ask for further information. However, it was thought possible that regardless of the conflict that experiments could be set up to test the truth or falsity of various statements concerning Wharton's Jelly, and that such testing need not be too prolonged to be effective.

20. Spermatoxins

As Dr. Folsome stated, theoretically this sounds excellent but it has never worked out practically. Dr. Hisaw thought it very unpromising, many people having tried it out without success. Discussion brought out the fact that there was no doubt of the possibility of the creation of antibodies to sperm or sperm proteins. However, the point at issue was whether such antibodies could effectively be used for fertility control.

19. Sulphydryl Groups

Dr. Hutchinson felt that sulphydryl inhibitors were likely to have extremely dangerous effects.

18. Sesame Meal

According to the material presented by Dr. Henshaw, experimentally its effect depended upon 70% sesame meal in the diet. This hardly sounds like a promising lead. Dr. Hutchinson also indicated that the active principal was likely to be an anti-metabolite, and both he and Dr. Folsome both agreed it would have many side effects.

17. Oil of Pisum Sativum

This was considered to be quite toxic, affecting both sexes and in the nature of a cytotoxin.

16. Soy Bean Hay

Dr. Folsome thought the activation was probably anti-enzymatic in action, and likely to have wide effects on general metabolism.

15. Ion Deficiency

This is considered impractical and dangerous. Dr. Folsome mentioned that apparently excess potassium ions may cause an increase in creatinurea, but he wasn't sure of the importance of this observation except to note that creatinurea also increased the frequency of anovulation. Apparently changes in a concentration of ions of copper, potassium and manganese have been considered. McCollum was able to produce oligospermia by means of varying the concentration of manganese, and he found an optimum range of the manganese ion concentration. As Dr. Hutchinson indicated, this may

lead right back to arginase with extremely large systemic effects.

14. Vitamin E Deficiency

Difficult to produce, probably impossible as a method of control.

13. Aminopterin

We need an analogue to Aminopterin which is less toxic before this approach can be considered promising. The question was raised as to whether the body had to deplete its folic acid reserves before the action of a folic acid inhibitor would take effect.

12. Arginine Deficiency

This was considered totally impractical in view of the fact that arginine takes part in so many of the body processes. An inhibitor or a large degree of deficiency would be extremely dangerous. However, no one in the group was expressly informed on this method. It was pointed out by Dr. Szilard that possibly one hope in this method of attack might be that it was the ratio of arginine to another amino acid which was important rather than the total amount of arginine.

11. Cholesterol

In view of the recent emphasis and data concerning sclerosis this method was felt impractical and not promising as an immediate lead.

10. Tetrazoleum Salts

Such salts inhibit the action of hydrogenase-dehydrogenase systems in the body and thus would have many side effects. These compounds also leave insoluble deposits at the site of their action. This method was considered very dangerous.

9. Furadroxyl, Furacin, Nitrofuran

These compounds were also considered as very dangerous and likely to have pronounced and wide side effects.

8. Phosphorylated Hesperidin

Information in confidence was placed before the Working Group concerning the recent use of this compound upon human subjects before sufficient animal experimentation had justified its use. The working group will await further information. However, it was felt by the group that this compound offered a very promising lead. Methods of experiment both in the laboratory and in clinics were outlined so as to determine the effectiveness, toxicity, dosage in both humans and monkeys. It was felt possible that the effectiveness of this method could be determined in a short time by a concentrated program.

Continued discussion of Methods 1 to 6 as led by Dr. Hisaw:

Dr. Hisaw continued his discussion of the pregnane series as started the day before. In answer to a question of Dr. Szilard's concerning the use of progesterone and related compounds as dietary supplements, he stated that all of the pregnanes tested tasted like flour and the taste would be no deterrent to their use.

He again stressed the solubility problem in research with the pregnane group. In answer to a question by Dr. Folsome concerning pellet implantation, Dr. Hisaw indicated this has not yet been done, that the results so far have been mostly by mouth. In general, the pregnane compounds have had relatively little work done on them in contrast to other hormones. Mention was made of the possibility of synthesizing progesterone rather cheaply. This was import-

ant because progesterone is a starting compound for synthesis of the whole pregnane series. The question of using sponges as a source of sterols for such synthesis was raised. Dr. Hisaw did not know precise details concerning this.

So far the only pregnandiol used is that from the urine of pregnant women which has not been thoroughly crystallized. We do not know how the synthetic compound would react in comparison with this impure substance so far in use. Most of the work done so far would have to be checked. One of the beauties of pregnandiol is that it has very few side effects and that it will compete vigorously with a number of other sterols. Pregnandiol will compete with progesterone in the rat but not in monkeys.

The two enzyme systems, one based on estrogen and the other based on progesterone, are very closely interrelated in action, but there is difference by species. They tend to act synergistically in primates -- not in rodents. Dr. Hisaw mentioned that aminopterin will inhibit estrogen in primates but not progesterone, but will inhibit both estrogen and progesterone in laboratory rodents.

One of the hopes for the use of pregnandiol is that it is an innocuous substance that may effect the pituitary to suppress ovulation. The nature of inhibition of the pituitary remains to be determined as a general principle. There are two important possibilities of the nature of inhibition. First is that inhibiting the pituitary is directly related to the number of sterol molecules; and the second is that the inhibition is relative to the physiological action of the sterols. If the last were the case, estriol would be less effective than estradiol. But if the first were the case, then estriol can be more effective than estradiol without having side effects. The same considerations apply to the use of the pregnane series, and, as stated before, once nature of inhibition is determined it will be possible to know exactly how to use pregnandiol.

Dr. Hisaw did not see much promise in prolactin. This is a pituitary hormone named because the first known effect was on the mammary glands. Prolactin has had many duties assigned to it in all aspects of reproduction. We don't know what its basic function is. We also don't know why it is in the male. We do know that it stimulates the secretion of progesterone by the corpus luteum. However, if prolactin is given during the luteal phase, it does not prolong the life of the corpus luteum, although the pregnancy urine hormone will prolong the life of the corpus luteum for awhile. We do know that prolactin is a protein. Dr. Hisaw thought that its use could only be in the remote future.

## Chemical Modification of Existing Hormones

It was mentioned that synthetic stilbesterol has about the same potency as estrogen. Dodds in England and Marrian in Edinburgh, Scotland, have been producing such synthetic compounds. These statements brought to discussion the point of chemical modification of existing formulas.

It was mentioned that it is not always necessary to have the phenanthrene nucleus as a prerequisite for physiological action in the sterols, that compounds with side-chains tacked onto a benzene nucleus have been produced which will have comparable physiological effect providing that the active chemical groups are at the same spatial distance from one another. Thus, effective organic chemistry could have a great importance in producing simpler compounds than we now have available and probably at much cheaper costs. As an example, stilbestrol is very cheap and there are several related compounds on the market.

## Cortisone

Some reproductive effects of cortisone have been noted but mostly in

rats and guinea pigs where abortion may be produced. Little knowledge of the action of cortisone on human beings in this connection has been found in the literature as yet, and its possible effect on ovulation is unknown.

Expansion of Existing Laboratories Doing Research on Monkeys

Dr. Hisaw mentioned that there are not many places where people are working on monkeys. Specific training is necessary to handle them, and in addition they are expensive. However, one of the cheaper ways of speeding up research work would be to make it possible to have more monkeys in the labs which now handle them and possibly to stimulate the development of other labs not now handling monkeys that would take on that kind of research work. In Dr. Hisaw's lab, they live in an air-conditioned room. The biggest cost is cages, although subsequent questions brought out that the cage and the monkey are about the same price -- roughly $40 to $50. (By ordering monkeys in lots of 50 or more directly from India they can be had for less than half this price.) Subsidy would also be to provide for more graduate students as half or full-time assistants. Dr. Hisaw pointed out in regard to his own lab the advantages of the university laboratory in regard to maintenance cost, in that the university will buy the feed, supply the animal, men to clean the cages, and because of the variety of research work being done at once, provide for maximum utilization of the monkeys. He also pointed out that the existence of clinical colleagues in the same area as the research laboratory facilities, makes it possible to have clinical consultation at all stages of experiment. He also mentioned the advantages of meetings once or twice a year for all those doing similar research.

Dr. Hisaw pointed out that there were dangers in overorganizing a research program at too early a stage. He made a plea for selection of research grant-in-aid funds on the basis of the caliber of the man rather than of the nature

of the result desired. He also stated that often it is difficult to quicken the rate of return from research regardless of how much money is spent, but that an organization with a clearing-house function might have an important stimulating and expediting function.

Other Methods

Dr. Hisaw indicated it might be useful to study the role of fructose in sperm maturation, although labeling it as a "timid suggestion".

PROCEEDINGS

Friday, September 5, 1952

In Attendance: Kingsley Davis, Paul S. Henshaw, Frederick Hisaw, William I. Lourie, Leo Szilard

Dr. Hisaw's Discussion Continued:

Dr. Hisaw explained to the less informed members of the Working Group the endocrine interrelationships in the developments of the follicle, the ovum and the corpus luteum. In answer to questions concerning the exact method of action of hormones, he indicated that although we know the general tissue response to certain hormones we have as yet very incomplete knowledge of the actual mode of action.

Dr. Davis asked Dr. Hisaw which approaches he would stress in general for our program and in his own research. Dr. Hisaw replied that the crucial point was the physiology of ovulation and of the menstrual cycle. A very delicate balance of hormones is involved. (As an example he mentioned that

if minute amounts of L.H. are given which are insufficient to cause ovulation the follicle will become atretic.) Careful study of follicular development is indicated. He also mentioned a group of related research studies in process now, directed at the relationship of the physiology of ovulation to the process of implantation.

In answer to a question by Dr. Szilard, Dr. Hisaw indicated that in intact monkeys there was wide individual variation in dosage response to pituitary gonadotropins when used to promote follicular growth and ovulation. As compared to other lab animals, there have been relatively few monkey studies. Monkeys are expensive, difficult to handle, and therefore used in but few places. There is as yet inadequate study to determine the hormonal balance and variation in individual animals. One method of approach is to use hypophysectomized animals -- which puts animals on a par in regard to any variation because of the pituitary. However, it is often difficult to consider such an operation in a $40 animal. Today, there is in the United States one remaining expert at performing this operation on monkeys -- Dr. Roy O. Greep at Harvard.

Dr. Szilard asked about inactivating the pituitary by means of X-ray. Dr. Hisaw indicated that although this might be done, it has not yet been done in monkeys. X-ray is difficult to focus, may effect other organs in the area, and is thus hard to standardize in contrast to surgery.

## One Ovary Versus Two Ovaries

Dr. Szilard postulated the eradication of one ovary by X-ray or surgery as a method of reducing the probability of having children -- i.e., partial sterilization. Such a method would not incur the opposition of the Catholic Church since intercourse would still have the goal of production of children but at a reduced probability. There was not complete agreement that such a

method would actually reduce the birth rate although it might. Results of animal experimentation do not support the thesis. At any rate, methods of control using mass X-ray or surgery in under-developed areas were not considered feasible even if possible. Dr. Hisaw indicated that by graded doses of X-ray to the ovary, a dosage has been found for rats and mice which destroyed all future oogenesis, but that the germinal epithelium then set up cords capable of estrogen secretion. Thus, at long periods, estrus was produced although a condition of permanent sterility prevailed.

## Abortion

Mr. Lourie asked if consideration of abortion should be included in our report, in view of its acceptance in places like Japan as a method of fertility control. General consensus was that the report could properly consider such an approach. Dr. Henshaw favored considering this even if only as a means of correcting mistakes in family planning -- failures of birth control. Some of the studies mentioned by Dr. Hisaw concerning the physiology of implantation would bear upon this subject.

## Anti-Gonadotropic Substances

In answer to a question concerning antibodies to gonadotropic hormones, Dr. Hisaw mentioned that this has been studied for a long time. Many of the results are not as much due to the reaction to a specific protein as might be expected. In some cases, one gets an antibody which is "anti-anything-human". That is, antihormone formation for human chorionic gonadotropin will also inactivate human pituitary gonadotropin.

The question of non-antibody but anti-gonadotropic compounds was raised. It is possible that lithospermum and maybe aminopterin may be in this class.

## Sperm Maturation

In reference to Dr. Szilard's interest in high frequency of copulation as producing immature sperm in the ejaculate with the effect of decreasing fertility, Dr. Hisaw mentioned that all of the sperm available are not ejaculated at any one time. It is true that sperm undergo ripening in the tubule of the epididymis and vas deferens and that in domestic animals too frequent mating does result in reduced fertility presumably due to immature sperm. However, in the guinea pig it has been shown that sperm from the proximal end of the epididymis (next to the testis) are as effective for fertilization as sperm from the distal end. The effect, if any, of copulation upon passage of sperm through the epididymis has not been determined. In the guinea pig it takes fifteen days for a sperm to travel down the nine feet of epididymis. Thus, it is likely that some mature sperm will be ejaculated despite the frequency of intercourse. Discussion disclosed wide species differences in total volume and concentration of sperm ejaculate. Mention was made of the "rebound" phenomenon as based upon either volume or concentration of mature ejaculate.

## Vasectomy

Dr. Hisaw viewed vasectomy as a simple, safe, and effective procedure in our society. He mentioned also that if only the vas deferens were tied off no hypertrophy and no atrophy of the testis resulted, and that spermatogenesis continued. Vasectomy on a mass basis was not viewed as feasible in areas such as India. Dr. Hisaw agreed with Dr. Szilard that methods involving control of male potency would work only in areas such as India which have a high degree of marital fidelity. In other areas, and in general, the most effective point of attack is the woman.

## Active Rebuttal Campaign

Dr. Hisaw felt that it was time to take the aggressive side in answering opponents of birth control. He was dismayed by the appearance in the press and on the radio of many statements, especially from the Catholic Church, which were absurd and easily refuted -- without the appearance of any rebuttal. Even though difficult in many areas to get such rebuttal statements into the press and radio, he felt that the time was ripe, or near-ripe, to stiffen the attitudes of at least the non-Catholic people in this regard.

Some discussion took place over the likelihood of getting some acceptance of certain ideas at the top level of the Catholic hierarchy and have consent filtered down to the parish level more or less as an official stand.

Dr. Henshaw outlined the policy of the Planned Parenthood Federation in this regard. This policy revolves about no direct antagonism with or toward the Church. A positive program is fostered on the basis that it is proper to study and effectuate fertility control. The Church must come then to Planned Parenthood with rebuttal.

In general, discussion disclosed uncertainty over whether a direct, positive program with implicit antagonism to the Church was timely or the best method.

PROCEEDINGS

Monday, September 8, 1952

In Attendance:

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|---|---|
| Kingsley Davis | Paul S. Henshaw |
| William Doering | Samuel Reynolds |
| Clair Folsome | Robert G. Snider |
| William Lourie | Leo Szilard |

## Phosphorylated Hesperidin

There was much discussion of this anti-hyaluronidase. However, it was decided that since Dr. Martin would be available at the Fertility Colloquium over the weekend, some of the members would attempt to get from him more information concerning phosphorylated hesperidin. Pending further information, however, the discussion was directed to the types of experiments on monkeys and humans which would determine the effectiveness, toxicity, and dosage of this compound.

The cost of the compounds was discussed. It was mentioned that the cost today is about $20 per pound. Dr. Doering stated that synthesis of the compound would not reduce the cost much below this figure. However, since the source is lemon and orange peels, it was felt that mass production would probably reduce the price, especially as the citrus people became interested in this possible by-product. Dr. Doering undertook to write to Dr. Sokoloff concerning his attempted synthesis of hesperidin.

It was agreed that phosphorylated hesperidin might be one of the leads of greatest importance at this time and should have high priority to settle the point of its effectiveness and toxicity. One suggestion was made that if phosphorylated hesperidin is eliminated rapidly from the body chemical alteration might provide a compound with a more prolonged effect.

Dr. Folsome outlined the rigorous type of testing done in commercial laboratories, which should be the prototype for the testing of any compound considered by this group. To test one particular compound, the following procedures are employed:

(1) four species (mice, rats, guinea pigs and rabbits) of experimental animals are used to test toxicity at five different levels of dosage.

(2) at the same time, studies are undertaken to attempt the method of action of the compound, such studies ranging from the simple

to the complex. He estimated that it would take from one to two years to undertake the above steps of analysis of one compound and that at least fifty animals are used for each series of tests, with the possible use of twenty animals for the intermediate stages.

(3) if significant clues are obtained as to toxicity and mode of action, then six primates are tested purely for toxicity. (Nothing on fertility control in all this.)

(4) the therapeutic index is determined by dividing the lowest toxic by the lowest effective dose. For any compound to be considered for use on human beings the therapeutic index must be at least 3. If the preparation is to be used orally, the index of such oral preparation must be at least five times the index of other routes of administration.

There are five things which it is necessary to know about a compound: 1) its effectiveness; 2) its stability; 3) its toxicity; 4) its availability; 5) (unremembered).

Discussion also brought out that such a screening program, necessary before clinical testing, is a very rough one. The screening tests used should be as close to the ultimate use as possible, but that since the nature of the program is that of screening and not of final testing, the inherent procedures in such a program a priori are simple rule-of-thumb methods.

It was mentioned that there is no one source which has coordinated all the screening attempts made in the past by industry and private investigators. Further, few records are likely to be found available for even one particular company indicating its results in such a screening program in regard to factors such as effect on reproductive process with which it was not originally concerned.

Dr. Reynolds mentioned that the Ciba Pharmaceutical Company, which has a good screening program, had found that about four thousand compounds had to be tested before they yielded one that passed the preliminary stages of acceptance for further study.

After all the above screening process has been done, the next process is to try out the compounds on young animals to determine chronic effects. Here it is possible that companies such as Ciba might have some references which would be useful to us if recorded fully.

Dr. Folsome mentioned the increasing use of bacteria as screening agents. By testing the action of specific compounds upon the various enzymes systems of different bacteria, it is possible to get an idea of the method of action of the compound rather rapidly.

The whole program on this process looks expensive. Qualified pharmacologists are high-priced. Out of about 400 companies only 20 do it.

The inadequacies of the screening process were shown by experience with chloromycetin which went through such a screening and yet turned out badly in regard to its latent effects in humans. This is an important point to realize since we are talking about a compound requiring chronic use.

It is somewhat naive to expect to find a "magic bullet" within five years. We need a long-range program starting with what we already know and the compounds we already have.

Patents - continued

Dr. Doering mentioned that under the patent law it is possible to patent a new use for an old compound. This has important repercussions concerning a future cheap contraceptive.

Naturally Occurring Anovulation

Dr. Reynolds mentioned the case of the summer monkey and the winter monkey. He stated that anovulation was common in the summertime in monkeys with no reduction in libido. Similarly, such anovulatory periods are common in adolescent girls up to the age of eighteen, and were frequent

in women at the other end of the reproductive age. He stated that these facts gave clues to basic research needing to be done to yield a natural method of regulating fertility. He stated that we knew little as yet about the mechanism of these naturally occurring anovulatory periods. Connected with this is the importance of light and other sensory nervous stimuli in certain animals in controlling the reproductive interests of the animal.

General Discussion - Continued

Dr. Szilard indicated that a desired type of process would be one that could be abused. We must expect people to forget to take the product one day and double or triple up on dosage occasionally. However, as Dr. Reynolds pointed out, it's hard to get something that will have an effect such as we wish and no other effect and still be completely innocuous.

Dr. Folsome indicated several ways to consider looking at the problem. One was to halt maturation; the second, to halt the union of the gametes; and three, the detection of ovulation. Both he and Dr. Reynolds figured that to have substantial progress we would need three types of research approaches -- short term, interim and long-range. It would be no trouble to solve the problem of the detection of presumptive ovulation. This is close to solution today.

Dr. Folsome mentioned that Pommeronke had demonstrated 17 amino acids in cervical mucous. Taurine was absent at the time of ovulation; lysine was diminished, and other amino acid changes were noted. He wondered whether the development of a colorimetric test were possible as a simple test for specific amino acids. If so, results could be determined in a method comparable to that of litmus paper. Women could take readings upon themselves. Possibly, by this method or that concerned with the fructosamine, or possibly the concentration of NaCl might enable the detection of ovulation forty-eight hours before its occurrence. Secretion of gonado-

tropins in the urine also offers similar test possibilities. If this is a situation where a protein and a carbohydrate are combined, Dr. Doering indicated that it would be a comparatively simple chemical task to provide a test which again could be reduced to a paper test. If a paper test were available, it could be made so cheaply that mass testing would be easily feasible. Such methods would also help many other types of research. It was estimated that certain of these tests could be developed within two years given enough resources, personnel and funds.

Dr. Folsome was also interested in the possibilities for long-range experiments indicated by observations that 87½% of the sperm head nitrogen is arginine nitrogen. Problems of arginine and creatinine metabolism are involved. He mentioned also that the mature sperm has a high concentration of prolamines, whereas immature sperm are loaded with histones. In no other place in the human body do we find such a high concentration of nucleic acids except cancer cells, the thyroid and the pancreas. Anti-metabolic compounds might be a possible area of investigation. Such long-range studies, for example, of methods for defeating arginine metabolism might produce results bearing upon alternate routes of muscle metabolism.

Certain ergotrates, with specific action upon the uterine muscles, seem to act by way of proline. It is interesting that a specific muscle is affected although similar types of muscle, such as those in the gut, are not affected.

Dr. Doering stated that there was very little room for imaginative work in chemo-therapy. The procedure in general was that as soon as one lead was obtained, compounds were varied in most minute and seemingly trivial ways. For example, there are hundreds of modifications possible in the alteration of estriol.

Dr. Reynolds indicated that if one chronically gave enough estrogen to affect ovulation in general, renal function and the action of adrenal cortex would become involved. Even if normal function is not impaired, usually more estrogen is given than is needed. Although theoretically it is possible to stay within the normal range, the variability of the menstrual cycle even in the same woman is so great that it is not practical to think of a general overall response with the same dosage. Here, Dr. Folsome indicated by diagrams overlapping phases of the menstrual cycle in the same woman.

Dr. Reynolds stated it was possible to modify the pituitary-ovulational rhythm in many animals by means of light, climate, etc. This is commonly known concerning chickens. In monkeys, the male will be received during the anovulatory periods of the female. Anovulatory periods are related to seasons. In some animals, a mating stimulus of some sort is necessary for ovulation. The spheno-palatine ganglion in the nose of rats and other animals can be stimulated with drugs so as to provoke ovulation. Pseudo-pregnancy follows anesthesia of this area. There's an old Egyptian belief that there is a relationship between the nose and the sexual cycle in women. Dr. Reynolds consented to provide a summary statement for the working group on these points.

In regard to the problem of production of anovulation in women, it was felt that this was a long-run research problem. It might take many years for solution, especially since no one is doing this sort of research at present. Geoffrey Harris is studying the neural pathways in the mid-brain in relation to normal pituitary function. No chemo-therapy work is being done even though Dr. Hisaw some time ago showed that the injection of copper salts in rabbits can produce ovulation, although the cutting of the nerve cells will stop this mechanism.

Some discussion took place concerning cancer as a parallel field; although a cancer cure does not seem to be on the immediate horizon, much has been learned which is useful. Dr. Doering doubted that the time was ripe as yet in either field. Drs. Folsome and Reynolds disagreed and mentioned the influence that Rockefeller had had upon sex research by subsidizing sex research in the '20's. In addition, it was mentioned that full knowledge of the physiology of the pancreas was not completed before it was possible to control diabetes. In the case of diabetes, control came before the relationship was remotely suspected.

Dr. Folsome mentioned anaerobic glycolosis in relation to sperm metabolism. Dr. Reynolds mentioned as a related line of research needing investigation that of the tubal and uterine secretions. He thought a simple line of research involving screening tests might be able to evaluate uterine fluid such as a method used by Sturgis some years ago in monkeys. The method needs only to be developed further to pharmacological effectiveness. Results would probably be forthcoming within five years. In other words, through study of the environment of the egg, we may be able to find some spermicidal agents that are effective by way of the maternal blood stream.

Dr. Folsome mentioned that present-day thinking casts doubt upon the sperm migration theory since uterine contractions have been proved to be of great importance. He indicated that choline seems to be involved and offers possibilities of fertility control by its inhibition and possible prevention of proper uterine contraction. Little attention has been directed at this area as yet.

When women get beyond the age of thirty-five, the number of anovulatory cycles increases. One of the easiest ways to control the bleeding that sometimes results is to give massive doses of yeast to aid the liver in metabolizing estrogen via the B-complex. In other words, an anti-B-

complex. In other words, an anti-B-complex compound resulting in increase in estrogen metabolism might produce anovulation.

Dr. Doering stated that it might be wise to separate fundamental from applied research. In the Ordnance program, for example, 5% of the budget is set aside for "basic research." Similarly, we might get in the position of supporting any good idea that has any implications concerned with fertility. Secondly, a program of applied research subsidy should be adopted for work on practical problems with a desired result within a short period of years. He thought possibly these two types of approach should be handled by different organizations. With this, Dr. Reynolds disagreed, thinking both types could be handled by the same overall agency so long as its general program was concentrated on control of fertility. The Guggenheim Foundation, by allocation of funds by men who knew the field as well as the investigators, had had great success in coordinating basic research in its selection of research projects. The group felt that if funds were announced to support basic research, the objective of fertility control should be mentioned to avoid being flooded with projects which would have to be rejected causing bad public relations.

It was also mentioned that an organization knowing the sort of research it wished done could have a liaison man go to well-established laboratories and stimulate interest enough to get the work done.

University seminars were suggested as a way of stimulating students, capturing their attention and of interesting their teachers in the problems of fertility control.

The question of a specific journal was raised. One limitation was felt to be that the average scientist does not wish to associate himself with an organization that has a mission. However, the establishment of a journal helps in creating a field. A journal in a specific field such as

fertility might have the effect for some people of effectively burying their scientific contributions; on the other hand, it provides a place where all interested could obtain the latest information on allfacets of the field. It was pointed out by Dr. Davis that in the field of demography the establishment of an English journal, specifically for this purpose, had had a stimulating influence despite the fact that almost any sociology journal would carry articles on demography.

It was mentioned that the Guggenheim people have been effective because they chose men and not problems. A difficulty is encountered in developing men with reputations in the field. Another difficulty is that of convincing men with established reputations of the desirability of work in this field. However, it was pointed out that the number of competent men in the field of human reproduction was increasing year by year.

It was felt that intercommunication of ideas is not a big problem. However, the question was raised, as earlier, whether even here it was not necessary to separate basic research from applied research.

Martin, Gustav J. and J. M. Beiler "Effect of Phosphorylated Hesperidin, a Hyaluronidase Inhibitor, on Fertility in the Rat" Science, 115 (2989): 402, April 11, 1952.

"Four experimental observations led to the currently recorded experiments. McClean and Rowlands (1) and Fekete and Dran-Reynals (2) have reported that the ovum in the fallopian tube is covered with follicular cells embedded in a thick viscous gel, chemically consisting primarily of hyaluronic acid (3). The sperm cannot penetrate the ovum unless the outer hyaluronic acid gel layer is dispersed. McClean and Rowlands (1) found that testicular hyaluronidase added to recently ovulated ova causes a dispersion of the follicular cells, denuding the ova and, thus permitting sperm penetration. Clearly, the mechanism is dependent upon the activity of hyaluronidase, and a highly effective inhibitor of hyaluronidase should

block fertility. In vitro and in vivo studies (5) have demonstrated the capacity of hyaluronidase inhibitors to prevent the follicle-cell-dispersing activity of rabbit sperm hyaluronidase and to act as contraceptives. Phosphorylated hesperidin (4) is a powerful inhibitor of hyaluronidase and is non-toxic. We therefore undertook to determine the capacity of phosphorylated hesperidin as a hyaluronidase inhibitor to produce sterility.

"The fertility experiments were done with rats, in groups of three, each cage containing one male, one control female, and one female being given phosphorylated hesperidin. In cages where the control females did not deliver, the results were not included in the final tabulation. This served as a check on the fertility of the males used. Females were examined periodically for vaginal plugs to insure that coitus had taken place. The phosphorylated hesperidin was given either intraperitoneally at 20 mg/kg or orally at 100 mg/kg. In each case the controls were treated with equal volumes of saline or water.

"The experiments were continued until two weeks after the last control delivery. At this time the animals were separated and treatment with phosphorylated hesperidin was stopped. The animals were kept under observation for a further three-week period, and were then remated with the males, this time without being given phosphorylated hesperidin.

"Phosphorylated hesperidin was found to be an effective anti-fertility agent, whether administered intraperitoneally or orally. In the group receiving the compound orally, 6 rats out of 30, or 20%, became pregnant and had successful deliveries. In the group being given intraperitoneal injection, 4 rats out of 24, or 17%, delivered. Thus, of a total of 54 rats, conception was prevented in 44. Since the cages in which the control rats did not conceive were discarded, the control rate has been 100%. In no cage where a control rat failed to conceive did an experimental animal become pregnant.

"Approximately 80% of the experimental animals became pregnant when they were remated after treatment with the phosphorylated hesperidin was stopped. The material when administered only to the males had no effect. Examination of vaginal smears showed that the estrus cycle remains normal during the administration of phosphorylated hesperidin.

"The results reported here, although striking, must be considered to be merely preliminary, because of the small number of animals used. Further work, with much larger numbers of animals, is now in progress.

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"Inhibition of Œstrus by Cultivated Gromwell"

By Dr. B. P. Wiesner and Prof. John Yudkin
Department of Physiology, King's College of Household and Scoial Science (University of London)

In one settlement of the Shoshone Indians, infusions of the roots of Lithospermum ruderale, Dougl., taken orally, were believed to have contraceptive properties.[1] Prompted by this, Cranston[2] administered fluid extracts of the herb to mice in their food. She observed inhibition of œstrus and fertility during treatment, without any evidence of general toxicity. Other workers confirmed these findings and also extended them by showing, for example, an inhibition of certain mammary tumours.[3,4] We have observed a

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complete inhibition of œstrus in mice of the C3H strain by aqueous extracts of Lithospermum ruderale administered daily for four weeks.

Lithospermum ruderale is not readily available and batches of this plant vary greatly in activity. However, we have found that English gromwell (L. officinale Linn.), which can be cultivated, yields œstrus-inhibiting extracts.

Cultivation. Seeds of wild gromwell were sown in February under glass, pricked off in 3-in. pots at the end of April, and planted out in May in open limed beds. Plants, including roots, were harvested in October.

Stabilization. We found that delay in processing or slow drying of wild plants tends to result in loss of activity. The cultivated plants were therefore dried at 60° C. immediately after harvesting. This procedure effected stabilization.

Preparation of extracts. The dried plants are finely ground and the powder is extracted with cold distilled water for 45 min. After filtration, the residue is re-extracted with water at 60° C. The second extract is cooled, combined with the first and freeze-dried, since there appears to be loss of activity in aqueous solutions even when they are stored in the cold.

Administration to mice. Tests were made on mature female mice of the C3H strain with high œstrus frequency, established by daily vaginal smears during a preliminary period of at least seven weeks. They received daily, by stomach tube, freshly made aqueous solutions of the freeze-dried extract. After preliminary experiments with herb-diet mixtures, this method of administration was adopted because of the uniformity of dosage and the avoidance of complicating factors such as reduced food-intake[4] and inactivation on standing. Smears were taken daily and showed that the equivalent of 1 gm. of the ground dried herb inhibited œstrus, cornification remaining in abeyance from the third day after beginning of treatment until four to five days after its cessation. There is, however, considerable variation in the dosage response; for example, reduction of the initial dose of 1 gm. to 0.5 gm. herb-equivalent daily may maintain inhibition of œstrus. No toxic or other side-effects were noted. After termination of treatment, the œstrus rhythm returned to normal within three days.

Administration to human subjects. Although gromwell has long been used as a medicament and for preparing a popular beverage, no ill-effects have been reported. The observations in mice also suggested that experiments in human subjects were permissible. Preliminary experiments were thus made with the small quantities of extracts available.

(a) Single doses of active aqueous extract corresponding to 10 gm. of dried herb per day evoked no subjective effects or objective effects in three subjects (two women, one man).

(b) A nulliparous woman aged thirty-four consumed, from the first day to the seventh day of the menstrual cycle, freeze-dried extract, equivalent to about 20 gm. dry herb per day; from the eighth day of the cycle until menstruation the daily dose was doubled. Indices of ovarian function, both œstrogenic and luteal, were recorded before, during and after treatment. These included vaginal cell content, characteristics of cervical

secretion, waking temperature and endometrial differentiation. There was no manifest change in the œstrogen response, but during treatment the ovulatory rise in the waking temperature was small compared with previous and subsequent records, and the progestational development of the endometrium was less than in the preceding and subsequent cycles. There were no other subjective or objective effects; for example, no changes in blood picture, urinary findings or pulse-rate. It would appear, therefore, that daily doses of roughly 20-40 mouse units did not inhibit œstrogenic secretion in the subject, but may have reduced the level of luteal secretion. The occurrence of luteinization is, of course, not incompatible with the suppression of ovulation. No risks of conception were taken by the subject during the treatment.

Our thanks are due to: Mr. W. W. Binns and Miss B. P. Jackson for pharmacognostic advice and preparation of extracts; Mr. John Gilmour and Mr. F. Hanger for collecting and cultivating Lithospermum officinale; Messrs. Ayerst, McKenna and Harrison, Ltd., for supplying extract of L. ruderale; Dr. Mary Barton for collecting specimens from the experimental subjects; Mr. E. C. Moran for presenting dried L. ruderale; Dr. E. N. Brand for carrying out bacteriological and other examinations; Mrs. E. N. Blacker and Miss Mary Jewell for technical assistance. The cost of these investigations was borne in part by a grant from Messrs. Kylon, Ltd.

March 25.

Statement from Dr. Reynolds --

The pituitary -- ovary -- uterus "axis" of reproduction in mature females is believed generally to be an autonomous and self-regulating one. Such is not the case, since extraneous somatic, and in the human at least, psychic stimuli can modify the pituitary-ovary rhythm. For example, it can be stimulated or inhibited by modification of daily exposure to light in certain birds and mammals. These mechanisms operate through optic-neurohypophyseal-pituitary pathways. In some animals (rabbit, cat, guinea pig, ferret, mouse, rat, hamster), stimulation of the vulvar, vaginal or cervical areas is necessary either to evoke ovulation or to produce pituitary stimulation resulting in luteinization in the ovary. The mechanism again involves neurohypophyseal-pituitary nervous pathways. In some species (mouse, guinea pig), stimulation of the spheno-palatine ganglion can modify the estrous rhythm. In clinical practice, a recognized relation exists between the nasal mucosa and menstrual rhythm, and emotional trauma can alter the menstrual rhythm.

In certain ungulates, transportation from below the equator to temperate climates north of it delays for one season the estrous rhythm. Rhesus monkeys in captivity normally have anovulatory menstrual cycles for four to five months a year. In most cases, not one fact is known about the physiological basis of these adjustments. If the mechanisms were known it would be feasible to consider what classes of drugs might mimic (in the case of anovulation or anestrus) or inhibit (in the case of ovulation or estrus) these responses.

PROCEEDINGS

September 9, 1952

In Attendance: George W. Corner, Kingsley Davis, William Doering, Paul S. Henshaw, William Lourie, Samuel Reynolds, Robert G. Snider, Leo Szilard

The first part of the meeting concerned the interruption of pregnancy in rabbits with the administration of estrogen. Dr. Reynolds outlined briefly the discussion that had occurred in previous sessions, and asked Dr. Corner's opinion of work of this type. Dr. Corner said that this was a relatively new thing and that few experiments had been done, probably only three or four (Csapo by). The present belief is that the interruption of pregnancy in rabbits during the first few days may not be due to tube blocking, as has been thought, but to the direct influence of estrogen on the egg. There are two hormones of the ovary which have a fundamental action on the life process. In the three or four experiments, the experi-

menters produced damage so real that it looks as though estrogen interferes with the viability of the fertilized egg. It may be that the potassium intake of the fertilized egg is influenced.

Dr. Szilard suggested that, with small doses of estrogen, you can stop pregnancy at once if you know the time of ovulation. Experiments would be most possible if we could determine exactly the time of ovulation in humans. Dr. Reynolds pointed out that we need the type of experiments that Pincus has conducted. One point which favors the theory of direct damage is that in rabbits, the fertilized eggs die before tube blockage can occur. An alternative is that death occurs due to a change of secretions in the tubes. Bishop would be interested in this. Dr. Corner considered that this question is minor compared to the general physiological problem having to do with the modification of pituitary-ovarian axis. The group was agreed on this. Further, the whole area of the chemical content of tubules and their action on the ovum needs study. It was pointed out, however, that the next step is to establish definitely what happens with rabbits. Experiments with monkeys, also desirable, are expensive and troublesome, partly due to their irregularity.

The difficulty of determining time of ovulation in humans causes trouble in human experiments. Dr. Corner felt that the temperature method of determining the time of ovulation is not reliable, but noted that Farris had had somewhat more success than usual. The time can also be determined in some cases by vaginal smears. In answer to a question by Mr. Lourie as to whether the spheno-palatine ganglion could possibly furnish a test for ovulation, Dr. Reynolds said that he didn't believe it could.

Dr. Szilard asked about the dosage of estrogen for humans, perhaps a small dose given for ten days, but Dr. Corner said he didn't know about the dosage; it is small for rabbits, however. Dr. Reynolds brought up the

fact that if small doses of hormones were effective in humans Helena Rubinstein's estrogenic cosmetic preparations, with apparent efficient absorption, would have had some effect in reproduction, but that it was difficult to know the significance of this because it is hard to ascertain the regularity of application, etc. That such preparations may be affecting fertility is possible. Dr. Davis at this point mentioned the fact that sterility apparently occurs rather frequently in the middle class group in this country in comparison to a place such as Puerto Rico. Dr. Corner agreed that study of hormone control of ovulation is a central lead.

This phase of the discussion was concluded with the agreement of all members that the physiology of the fallopian tubes and their secretions is not very well known at this time, and that this area deserved development.

## Various Possibilities

Dr. Corner was questioned about pregnandiol, which Dr. Hisaw had discussed, but he stated that he had no information on the subject. Dr. Szilard mentioned the possibility of administering estriol, which is a weak estrogen hormone, to males if it could be done without feminization, and Dr. Corner felt that it might be possible.

Dr. Davis at this point requested Dr. Corner to give the group his ideas about the most promising directions, in the order of their importance. Dr. Corner said that he saw no hope for early success in any of the leads brought up so far. They are all in very early stages of experimentation, and he felt that there was little hope for any results in less than five years, unless it were a case of eliminating poor leads quickly. He suggested, in fact, that this might well be the best way to proceed.

## Immunization.

Langer's experiments in immunization with Wharton's Jelly, were a

point in question. It was pointed out that he had worked under admittedly inadequate facilities in Cuba, and that his publications had appeared in relatively obscure journals. (He was trained in immunology and cytology in Vienna and had to leave for political reasons, so that as an expatriate scientist, it is not necessarily to his discredit that his work in this country and Cuba should not be well known.) Dr. Corner's feelings were, however, that in his papers he had implied that he was dealing with well-established premises, whereas there is actually very little in the medical literature about this problem. Dr. Corner thought it might be possible to determine within a year the worth of Wharton's Jelly.

It was also brought out that immunization in general is a delicate matter, as in the case of the Rh factor, because of the possibility of damaging rather than killing the offspring. Dr. Szilard stated this involved abortion, not prevention.

In the case of Rh, the mother is immunized by her own offspring when she is mated with a father who carries the immune bodies. A leak through the placenta is involved. The immunization builds up in time, so that each successive child is more dangerous. The same principle applied that was mentioned above; viz., the process produces sick babies, not dead ones.

The advantage of immunization is that it would last for some time. But, on the other hand, protein immunity is notoriously precarious.

Spermatoxins.

The question of spermatoxins, which purportedly cause the woman to be immune against the sperm of a specific man, was brought up. Dr. Corner said that he didn't know much about them; Dr. Reynolds reported that something had been done under the Department of Physiology at the University of Chicago in the late 1920's. At the time, it seemed as if there was

something to it, but a later reevaluation was done with negative results. Friedman, who is now in Washington, and McCarthy were the people who worked on the evaluation.

Phosphorylated Hesperidin.

Dr. Doering reported that he had looked into the question of the cost of the phosphorylated hesperidin, and that it was very cheap. Eight per cent by weight of a dry orange peel is hesperidin, and the isolation procedure is simple; it involves drying the orange peel and extracting the substance with water or a mild caustic (carbon dioxide, e.g., can be added, allowed to stand, and the crystals form).

Grants-in-aid versus Institute Again

Dr. Corner was asked his opinion about these alternatives (and if they should be alternatives) and was also asked to speak in terms of his experience on the Committee on Sensory Devices. Dr. Corner outlined the history of this committee. It was started by Dr. Bush in order to work on prosthetic devices for the war-wounded and reading aids for the blind. The former turned out to be a reasonably simple job, and with good engineering, mechanics, and orthopedic surgery, they were successful. The problem of developing a guide machine to aid the blind in reading, an obstacle finder, and something for people with limited vision, was more difficult. A committee was appointed with Dr. Corner as chairman, and members from various fields were chosen to serve on it. As in the case of other OSRD projects, a central laboratory was chosen and placed under contract for experimentation. The committee in time grew to be largely a board of trustees for a laboratory. In addition, the job turned out to be virtually impossible. Dr. Corner expressed the view, based on this experience, that

the employment of people in a central scientific laboratory succeeds according to the quality of the people in the laboratory. The danger is that the scientific advisors eventually tend to abdicate their own scientific judgment to that of the people under contract in the laboratory.

Dr. Reynolds asked Dr. Corner if he felt that grants-in-aid would bring results more effectively in the field with which this group is concerned. (Dr. Henshaw pointed out that there were three levels involved in this field, animal experimentation, bio-chemical research and clinical testing.) Dr. Corner replied that there were two principles involved in this work which would affect the answer to the question. The first is that ours is such a diverse field that it may be necessary to draw in almost any science. The second factor is the nature of the aim, that is, is it pure or applied science? The NRC committee on problems of sex was and is nearer the pure research end of the scale, and involves general principles of biology with fairly little direction from above. At the other end of the scale is the atomic energy work which, without organization, would never have been accomplished. However, Dr. Szilard pointed out the great danger of too early organization, saying that if the government had entered the picture six months earlier, there would never have been an atomic bomb. The direction became advantageous in the case of engineering problems, but even in this case a high degree of organization did not always pay off, especially in the early stages.

Dr. Corner felt that the creation of a special institute in this case would be premature. He also felt, however, that grants-in-aid were not a solution necessarily because the people who come forward are not necessarily working on the problem we are concerned with. It would be necessary, in our program, to pursue a path between the two extremes discussed.

Dr. Corner felt that there is a good bit of humanitarian appeal

involved in the question of fertility control, and some scientific appeal. It would be necessary to get a man of considerable scientific versatility as liaison officer, choose some good leads, and capitalize on the enthusiasm of those people who are interested rather than insisting on investigators of established reputation. A recommending committee and an executive officer could act as an expediting agency.

Dr. Henshaw pointed out that some specific things can be handled on a small grant basis. Others, like hormone controls, require a sort of program and an institute. Dr. Corner added that clinical testing is an enormous enterprise. It also has difficulties, but might be done in India, by government initiative perhaps.

In order to get a more exact idea of what could be accomplished in a given situation, the question was raised by Dr. Davis as to what could be achieved with a laboratory of about 16,000 square feet and a staff of seven people. Dr. Corner felt that it would be difficult to give an exact answer to such a question, but he did say that, under such an arrangement, Langer's immunization work with rabbits could probably be tested in about a year. (It was also pointed out that experiments and tests in foreign countries could be planned.) Dr. Reynolds made the suggestion that various screening tests for the reproductive functions would be made in such a laboratory and that, often, such tests eventually are reduced to a technical level not requiring the service of professionals. At the same time, it would be necessary to have a certain amount of prestige and favorable location, such as a university or medical school connection. Dr. Henshaw asked if a connection like the Sanger clinic would serve this purpose, but Dr. Reynolds felt that that would be less desirable than a hospital or university connection.

Dr. Davis pointed out one advantage of an institute, whether or not it was working independently, and that is the fact that there would be a staff

working full time on this particular problem. In a contract laboratory, the staff would expect to work only part-time on this question. Furthermore, it would expect to be shifted in time entirely to some other research problem. There would thus be a certain distraction and lack of career opportunity in fertility control research which would not be present in a special research institute.

Dr. Szilard maintained that it is necessary to have some group which wishes to see this thing through. It is not always possible to farm out contracts. The program will need young men, perhaps on five-year contracts. A small institute could act as a catalyst. One-third of the budget of the total program might be devoted to the institute or laboratory, and 2/3 could be used for research in established centers like Johns Hopkins University and Harvard. (This would be based on a five-year plan with a budget of about ½ million a year.)

Dr. Reynolds suggested that such an institute might act as a kind of strategy board; both Dr. Davis and Dr. Corner felt that it would be best to have a strategy board different from the institute staff. Dr. Corner pointed out the dilemma involved in such a situation; viz., that if good people were brought in to plan the strategy, they would want to work on general problems and not be too narrowly circumscribed.

Dr. Reynolds mentioned the work of Houssey in Buenos Aires, who does good work but has very little support. The group was agreed that something might be gained by working with such persons. Dr. Corner pointed out the danger of propaganda concerning American attempts to reduce population in other parts of the world. Houssey, however, might be all right for contract work. It is necessary to be very careful under a Peron regime, for instance, not to seem to be getting aid from a foreign country. The point was made that it is also necessary to be careful in regard to the

Catholic Church, but Dr. Szilard was of the opinion that they are not interested at the research level, but only when application comes in. It would be possible to organize a Latin-American division, perhaps.

Dr. Corner said at this point that if there was enough money to do several things at once, he would withdraw his objection to an institute. Such an institute could certainly do research that it would be hard to get first-rate pure science laboratories to do. Dr. Corner said, for instance, that his laboratory would not be interested. It was still agreed, however, that it would be highly desirable to be as close as possible to a major university or organization. The point was again made that it is difficult to keep scientific personnel in a purely applied institute.

Dr. Reynolds mentioned the Institute for Applied Biological Science in Texas (Tom Slick) and the difficulty they had due to the pressure to work only on the applied aspects. They were working on problems of livestock, and the backers wanted to see financial return at every step of the way.

Dr. Reynolds brought out the fact that a kind of scientific prostitution took place when there is liaison between a basic scientist and a commercial group. It is hard to get commercial support for research on products applicable in foreign areas. Dr. Doering pointed out that so far as the pharmaceutical houses were concerned, there is more money in cows than humans, so to speak.

The question was raised by Dr. Corner as to why Ortho had not made more important discoveries, in view of the good leadership of Hartman. The feeling of the group was that the time was not ripe. When it was mentioned that penicillin development had progressed rather rapidly and had considerable support, the group was reminded by Dr. Szilard that the government had put up money. Also, its profit-making potentialities were recognized as well as its effectiveness.

The Ortho lab was established in the late 1930's, when it already had an established business in contraceptives. The company wanted to "work both sides of the street" in the field of fertility, as Dr. Reynolds put it, for prestige purposes. He also pointed out that a good deal of money has been available for research in the hormone field. The pharmaceutical concerns are attempting to work within the framework of our society, on needs as consumers see them. In this case, it is infertility in the U.S. Because of the interest of the middle class in our society in overcoming sterility, for example, a ready market exists for products that will help in this respect. There is not a comparable demand for new methods of fertility control in the United States.

Johnson & Johnson is a conservative group. They have given evidence of being unwilling to spend much money on research, but rather prefer to invest in projects with an assured outcome.

Dr. Henshaw noted that the target of this working group, if achieved, would put some of these companies out of business. This may account in part for the lack of achievement on the part of companies like Ortho.

Dr. Doering asked Dr. Corner if investigation on lithospermum would be classified as pure or applied research. Dr. Corner felt that it would be applied if it involved the effect of one product on the pituitary gland. Dr. Doering then pointed out that it might lead to basic problems, but Dr. Corner said that, even so, it would take working time away from the applied problem; by working on the problem from the standpoint of organic chemistry; for instance, the researcher would necessarily be less concerned with the contraception angle.

## NRC Committee on Human Reproduction

In discussing this committee, Dr. Corner stated that the Planned

Parenthood Federation, at the instigation of Dr. Dickinson, had planned to raise money for basic research, and to give it to the National Research Council committee. The Chairman of the Committee was Dr. Howard Taylor, Jr. It was to function on a grant-in-aid basis. During the course of its activity, however, there was some misunderstanding over the basic vs. applied research issue. In addition, the Planned Parenthood Federation was not able to raise the substantial funds hoped for. (Dr. Henshaw pointed out that the money dwindled in part because of the misunderstanding over basic policy.) The committee spent $35,000 per year in the last five years. Dr. Corner pointed out that it was partly a failure in the realm of human relations, and that the NRC could have handled it better.

Initially the program was coolly received by Osborn, Notestein, and Emerson. People who had the money to give felt that they weren't getting the program they wanted, and the scientists were concerned with saving their reputations. In answer to the question as to whether the formation of the group was premature, and that this may have been part of the trouble, Dr. Corner said he didn't think so.

Dr. Henshaw, who had gone through the list of grants and applications for grants, said that many of them were quite mediocre, and most for fairly small amounts. There were a number of good people applying, but the committee in general wanted to support a number of different projects and perhaps make up for the mediocrity of some by maintaining a certain breadth of program. It was felt that, on the whole, the program didn't do much in the way of stimulating activities.

Dr. Doering asked Dr. Corner's opinion about the calibre of men applying for grants and Dr. Corner replied that he didn't think they were up to standard of those who applied to the NRC Committee for Research on Problems of Sex. The history of this committee, which was more successful, will be

published in a few months. Dr. Yerkes went out and stimulated research, and overcame the taboos on the subject matter. Dr. Davis pointed out that this same type of taboo now exists in regard to birth control. Dr. Reynolds said that the job of removing the taboos must be considered as a mission. (In answer to the question of how Rockefeller got into the Committee on Human Reproduction, it was mentioned that this occurred through the Planned Parenthood Federation.) It was also mentioned that syphilis research has now become respectable -- Dr. Reynolds noted that Allen's book, Sex and Internal Secretions, had marked a turning point, in fact a landmark, in the attitude toward the field. This illustrated, according to Dr. Henshaw, the need to create a field. The idea of publishing a journal in this particular field to stimulate scientific interest was mentioned again. Dr. Corner thought the field too narrow. Dr. Reynolds suggested that a review journal might be in order, but not one which contained original articles.

Dr. Szilard pointed out that our enterprise is not limited simply to the control of conception, but it is concerned with fertility. A special journal would take bio-chem articles significant for fertility control but which were of no real interest to biochemists. It would help to produce a new group of people who would have a common goal. The group as a whole felt that the question of a journal was not a problem which needed early consideration. Dr. Doering added that it might do more harm than good to start a journal and force results for publication, so to speak; in this way the field might get a black eye before it was well-established.

## Financial Arrangements

Dr. Davis pointed out that the problem here was different from that of the Committee on Human Reproduction or Sex Research ($80,000 was the most the Committee on Sex Research ever had). It was agreed that large

sums can be expended in a broad field, but in a narrow one, it is more difficult to invest the money. The investigation of basic principles is not a sufficient goal -- it is necessary to set up a system for developing new prospects.

## Direction in Which to Move

Dr. Davis asked Dr. Corner what, in his opinion, are the chances for success and whether they justified the needed expenditure. Dr. Corner felt that there was less than one chance in 100 for any success in the next five years. Dr. Szilard felt that anything with a probability of less than 10% could be regarded as a miracle. Dr. Doering asked if a sort of chemo-therapy institute like Sloan-Kettering was under consideration. (This would probably be on a large scale.) But, as Dr. Szilard pointed out, the scale does not affect the ratio of money to achievement. Dr. Reynolds added that it does, however, affect the time. One does need to operate on a large enough scale so that "accidents" can happen, because frequently, significant results are turned up by just such accidents. Dr. Szilard felt that, in general, we tend to underestimate the probability of the improbable. Dr. Reynolds pointed out that frequently, when an organization encouraging a specific development finally does withdraw its support, the investigators are just on the verge of discovery. An example of this was the putting of oxygen on the eleventh carbon atom of a sterol. Merck was working on this problem and decided to stop, and the investigator continued his work on his own and about three years later achieved success.

Dr. Davis pointed out the need for motivated research -- that the chances for this problem of fertility control being solved in time are good, in fact, about 100%. The question at hand is the type of program

needed to further the development which is necessary; specifically, whether a $10 million program would hasten the overall solution. Dr. Corner felt that if a program were directed only at general research on reproduction, the outlook was not very hopeful as far as early results (10 years) were concerned. If, however, specific problems were attacked, he felt that there was a real possibility. In answer to Dr. Davis' question as to the most promising lead, Dr. Corner said that it will probably be easier to stop spermatogenesis than ovulation.

## Antihistamines

Dr. M. C. Shelesnyak, Weizmann Institute of Science, Rehoveth, Israel, reports informally that in mice, fertility may be reduced from 95-100% to 20% by using antihistamines in pregnant mice prior to and at the time that a fertilized ovum reaches the uterine cavity. Presumably it prevents the first hyperemia (a "histamine" response to a fertilized ovum) which is an essential step in the formation of the maternal part of the placenta (decidua). Consequently the ovum withers and dies. Dr. Shelesnyak says:

> Since then, I have completed a study, now in press (Amer. Journal Physiology) which leads me to suggest that the release of histamine may be the provocative agent in initiation deciduation. I have (unreported) been carrying on some studies in the mouse, and when Benadryl is administered, subcutaneously, on day 3- 4- 5- 6-of pregnancy (using sperm or plug as check point), either separately or in combination 3- 4- 5- and 4- 5- 6-, I find a reduction in carrying on to term - of about 80%; that is about 20% deliver. Controls are about 95 to 100%. Since I feel that the answer should be 100% inhibition, I am continuing the task using longer acting antihistamines, and more frequent, injections, over more specific time areas. Preliminary (very much so) trials in rats are not as striking, but here too I feel if I get the proper drug and dose, a one-shot administration should block decidual formation and subsequent development.

## State Mental Hospitals and Sex Research

By telephone interview with Dr. J. B. Hamilton, Professor of Anatomy, State of New York College of Medicine, Brooklyn, the following information

was obtained concerning research work done in state institutions for feeble-minded.

In some, sterilization by gonadectomy or tubal ligation is permitted or required by law. Medical directors are frequently cooperative in making this material available for clinical investigation. The following leads were given:

New Jersey: institutions are available and there is interest in investigation, but experience shows that conservatism prevents utilization of this material.

Massachusetts: For many years there has been a research program at the Worcester State Hospital for the Insane. The recent director, Dr. R. Matthew Klein, is most cooperative in encouraging sex studies.

New York: Dr. Klein has accepted the position of director of a new hospital in Rockland County, New York.

Kansas: For years, Dr. Hamilton has had a program of sex studies going on here. The new medical director is one of Dr. Hamilton's group. Castrations are done in men, and oöphorectomy or salpingectomy in women. However, a "storm" is blowing over at the moment regarding operations on women.

Dr. William Greulich, Professor of Anatomy, Stanford (now scientific attache at Bonn) told Dr. Hamilton of state mental institutions where clinical observations and investigations could be made in relation to gonadectomy or tube ligations. These are Vermont, Oregon, and Texas. The last is particularly valuable for potential work.

Illinois: Dr. Himwich has within the year accepted the position as Director of Research in a state institution at Galesburg built expressly for the purpose of doing clinical investigation. Dr. Himwich has expressed a desire for cooperative work with established institutions and organizations.

(S.R.M.R.)

Excerpt from a letter to Dr. Paul S. Henshaw from Stuart Mudd written September 8, 1952:

"The possibility of obtaining temporary infertility in experimental animals by active immunization of the females with parenteral injections of sperm was investigated critically by Drs. Werner and Gertrude S. Henle in the writer's laboratory in 1936-1939. Reprints describing these studies are going forward to you under separate cover. Spermatozoa were shown to possess tissue- as well as species- specificity and iso-antibodies were

successfully elicited against them in guinea pigs, rabbits, rats and mice. However, under no experimental conditions tried did the fertility of the females in whom iso-antibodies were induced show appreciably change from the normal. Review of the literature on so-called spermatoxic immunity in relation to fertility did not reveal any instances of induced temporary sterility which stood critical analysis. Both Drs. Henle and the writer felt that the subject had been dealt with sufficiently thoroughly so that further effort along these lines with the means then available did not seem worthwhile.

"In the years intervening since the Henles' work the use of adjuvants in immunization, particularly under the leadership of Dr. Jules Freund of the New York City Public Health Research Institute, has opened up the possibility that a higher degree of immunity might be elicited with the aid of adjuvants, and that such immunity might possibly cause temporary infertility. This possibility is of much theoretical interest, and should it be realized, active immunity might possibly become a practically useful procedure for a limited category of cases, wherein expense was not a limiting factor and where strict medical supervision could be insured. For mass fertility control of backward populations, however, it is hard to imagine that immunization could ever be economically feasible or medically safe. Beside the obvious dangers of uncontrolled injections of homologous cells, there has been a recent suggestion that serum hepatitis may be transmitted through semen. Should temporary sterility be shown to be possible using heterologous sperm, then dangers of allergic sensitization and other complications would have to be guarded against, all of which would require highly expert supervision and be very expensive."

PROCEEDINGS

Thursday, September 11

| In Attendance: | | |
|---|---|---|
| | David Bishop | William Lourie |
| | Kingsley Davis | Samuel Reynolds |
| | Paul Henshaw | Leo Szilard |
| | Michael Heidelberger | Albert Tyler |

Immunization

Dr. Szilard started the discussion by briefly summarizing previous discussions concerning the possibility of using immunization as a means of controlling fertility, and Dr. Heidelberger was asked to give his ideas as to the feasibility. The latter pointed out that some work has

already been done in this field by Emily Loeb and A. Knowlton. Sera obtained from rabbits immunized against rat placenta was found to damage rat kidneys. No attempt was made at fractionation. Dr. Heidelberger was not certain how many species had been tested, so that much may yet need to be done especially in regard to monkey experimentation. However, a close relationship between the kidney and placenta was definitely shown. Work is still going on at P&S. It was pointed out that in order to use the immunity principle for fertility control, it would be necessary to find a protein in the placenta that is not present anywhere else in the body.

The question was raised as to the immunization effects of Wharton's Jelly -- Dr. Reynolds stated that the jelly consists of several different substances. There is no adequate proof that the "jelly" is species-specific. Hence it cannot be guaranteed to have always a unique effect in immunizing alone. As in the case of any blocking, you get constriction of the arteries and veins. Dr. Bishop pointed out that polymerized hyaluronic acid was involved in this reaction.

Dr. Heidelberger said that a book by H. Gidson Wells contains a section on Wharton's Jelly. Some work was also done by Hektoen and Welker, but he was not familiar with the results. Dr. Bishop asked if the peritoneal fluid could be used for the production of antigens. Dr. Heidelberger's opinion was negative.

Dr. Heidelberger said that Jules Freund of the New York Public Health Research Institute has worked with anti-sperm sera, and has sensitized male animals against their own sperm. He used adjuvants to increase the strength of the reaction. There is strong evidence of degeneration in the experimental animals used, and also irritation of the testis. Tubercle bacilli were especially useful as adjuvants. It is a well-established

principle that the immunity lasts longer when the baccili are included in the injections. This is, of course, a male method.

Dr. Bishop pointed out that there was some work done on rabbits at Johns Hopkins, and the publications show evidence on both sides of the question. He also pointed out that the Russians have done some work in isolating spermosin. They were able to find some of its chemical properties, but nothing has been done recently. He felt that this should be looked into. One of the problems is that it requires great amounts of sperm. (The work was done by Englehart.)

Dr. Henshaw asked how the tubercle bacilli act along with the sperm, and Dr. Heidelberger answered that with the mixture you get a prolonged and intensified antibody effect. The general principle has been used many times; a combination of antigens seems to work better. With typhoid bacteria you get ten times the titre and a much longer effect with adjuvants than with typhoid bacilli alone. Spermatogenisis was actually stopped, varying according to the dosage and species.

The group was agreed to invite Dr. Freund to come in to discuss his work.

Dr. Henshaw suggested that some of the impurities may have been acting as adjuvants in some of the previous, partly successful experiments on immunization against sperm or Wharton's Jelly.

Dr. Szilard then asked about the possibility of immunizing females against sperm. Dr. Heidelberger answered that you might be able to produce antibodies capable of immobilizing the sperm. Dr. Szilard then asked whether, since there is no testis in the female, other organs would be damaged. Dr. Heidelberger replied that it depends on the way the material producing antibodies was given. He pointed out that it is very important to do these tests thoroughly with animals before doing human

experimentation, but that ultimately it must be tried out in human beings rather than between species.

The question was raised by Dr. Henshaw as to whether it is likely that you can get the immune bodies into the cervical tissue, where they can get at the sperm, if they are in the blood first, for instance. Dr. Heidelberger said that there is some evidence that this can be done. Cervical mucus has not yet been studied from a serological point of view. However, he pointed out that you can't reason in quite that way.

It is conceivable that the ovum itself might be made to bear an antibody, since it contains protein.

Wharton's Jelly is of embryonic origin. The question was raised as to whether it could be different enough from the mother to form an immunity in her. Dr. Heidelberger pointed out that this does happen in the case of Rh, where there is a different blood group factor in the embryo than in the mother. The damage occurs rather late, however. Dr. Reynolds said that by analogy you would have to admit that there could be a comparable mechanism at a different time.

The group agreed that there was in this approach a possibility for fertility control, but that it would take considerable work to establish its applicability. Dr. Heidelberger felt that the idea of immunization is a good one to work on.

Dr. Henshaw read an extract from a letter from Werner Henle and Stewart Mudd . . . .

Dr. Heidelberger also felt that the question of the use of adjuvants should be followed up, but that sensitization throughout the organism must be watched very carefully. Immunization would not be an impractical method of fertility control if developed, because vaccination and inoculation have been widely accepted in backward areas. Dr. Heidelberger felt

that Dr. Mudd was perhaps too pessimistic in his letter with reference to the possibilities of this approach for underdeveloped regions.

Mr. Lourie brought up the possibility of getting more powerful mixed vaccines in time by adding more bacterial adjuvants.

Dr. Heidelberger said that in malaria it frequently happens that a human develops antibodies to his own broken blood-cells. He felt that there were possibilities of using endogenous proteins in fertility control methods.

Dr. Szilard asked about the possibilities of changing weakly antigenic natural proteins by adding chemical groups so as to produce higher titre. Dr. Heidelberger answered that although it was possible, one ran the risk of transferring the antibody reaction to the foreign grouping introduced, and not increasing the response toward the normal antigen.

Dr. Davis then asked about the order of experimentation; e.g., if it should be tried on rodents and monkeys and then humans. Dr. Heidelberger pointed out that guinea pigs show sensitization par excellence, and that if it did not occur in them, it probably would not in humans. The principles should be worked out with rodents, then tried on monkeys. Only later should human beings be used.

Dr. Bishop noted that the building of sperm antisera was implied here, and asked if it would be reasonable to see if such an antisera against the egg, or even one against a substance in the egg, could be built up. This is suggested by the serological nature of egg and sperm reactions. Dr. Heidelberger stated that the difficulty with this is that a good many embryonic tissue proteins are undifferentiated, so the young embryos give no antigenic response. Dr. Bishop then said that it might be possible there would be something specific in the zona pellucida which might inhibit contact between the egg and the sperm, and Dr. Heidelberger thought that there might be a good possibility of this.

Dr. Henshaw asked how long it might take to work out the problem of immunizing the female in such a way as to make her infertile. He thought that in about two years it might be done. He pointed out that help would have to be obtained from many different fields -- physiology, pathology, histology, immunology, biochemistry, etc. A laboratory would not necessarily need to furnish a specialist in each of these fields, but the work would have to be done where all could be available, as in a medical school, for instance. An expensive laboratory would not be necessary, but certain desirable equipment, such as an electron microscope, might cost a great deal.

Dr. Davis asked if it wasn't true that the research would not get done without some kind of stimulation. Most research in immunology, for instance, is done with respect to disease prevention. Dr. Henshaw pointed out that more work was done in the 1920's on immunizing females than has been done since. Dr. Szilard felt that the idea of immunizing the male was likely to cause trouble. Dr. Heidelberger felt that the stimulation of our group might come in with regard to Henle's work with adjuvants, for instance. Henle might be stimulated to repeat his work with adjuvants.

Dr. Davis pointed out that the group had been speaking primarily of sperm, and asked if anything was possible with the other constituents of semen. Dr. Bishop said it is harder to immunize with seminal plasma. Dr. Heidelberger stated than an antigen in particulate form is usually better than the same one in solution.

## Fertilizin

Dr. Bishop then spoke of the work he had been engaged in at the California Institute of Technology. He mentioned that Dr. Tyler's work

with invertebrates was analogous to the work at California Tech. with vertebrates (rabbits). There is an anti-fertilizin mechanism operating in invertebrates; a muco-protein (fertilizin) in the egg jelly reacts with the anti-fertilizin in the sperm, and the sperm is not fertilizable. An agglutination reaction causes the sperm to clump. In certain instances, there is spontaneous reversal, but after agglutination the sperm are no longer capable of fertilizing the egg. However, the clumping problem is really incidental to the question of what takes place when the sperm hits the egg. The mechanism by which contact is made is agglutination. If you neutralize fertilizin and cause partial infertility, you can increase the fertility with more fertilizin. There is a good correlation between the fertilizability of the egg and the amount of its fertilizin. The mechanism is like the antigen-antibody reaction. Sometimes there is a reaction but no clumping. This depends upon whether there is a univalent or multivalent type of binding.

The technique used with vertebrates is different from that used with invertebrates. The egg is put on a slide and watched under a microscope for the agglutination when sperm approach. Rabbit eggs are hard to secure. Clumping is definitely observed in the rabbit observations. As many cross-species tries as possible were made. There is some species specificity. One unsolved problem is what makes the egg release its fertilizin. The reaction is stronger the older the egg, so long as the zona pellucida is still around the egg.

Dr. Bishop said that he did not yet see any application to our problems in these findings except insofar as one might look for egg substances to produce immunization. There seems to be a basis for serological reaction in egg and sperm. It has taken twenty years to get at the egg-sperm

relation in invertebrates, and it is hoped that it will not be necessary to spend so much time on the vertebrates. It's possible that there are some short-cuts. Apparently there are uterine secretions which agglutinate sperm. This would be abnormal, but the phenomenon does occur in rabbits.

Dr. Reynolds pointed out that some male rabbits simply do not impregnate certain females. When he is breeding the animals, he frequently has to mate a female to two or more males before achieving impregnation. Dr. Davis noted that the same type of "mating incompatibility" occurs in humans, for which the explanation is not known. Possibly abnormal agglutination is involved. These thoughts give a suggestive lead as far as humans are concerned -- the uterus might be studied with the possibility of agglutination and antibody reaction in mind.

Dr. Bishop pointed out that the source of the best aggultinins is inside the sperm. There is, therefore, the possibility of finding materials that will be carried by uterine secretions which will agglutinate the sperm since sperm are rather readily agglutinated. It was noted that antifertilizin can be extracted from invertebrate sperm. The suggestion was also made that this type of study might be done with the added use of adjuvants.

Dr. Szilard noted that it is apparently difficult to immunize invertebrates, but that there might be the possibility of using fertilizin derived from invertebrates in vertebrates to produce antigens. It has been difficult to demonstrate the existence of fertilizin in vertebrates and according to Dr. Tyler there is as yet no evidence that vertebrate antibodies against invertebrate fertilizin will act on vertebrate eggs.

The suggestion was made that one might use cells surrounding the egg as material to produce antibodies. Follicular fluid in rats presumably can be derived from the outer part of the egg. In many invertebrates, fertilizin-anti-fertilizin reaction does not involve agglutination (e.g., starfish). This may be true in mammals also. By adding a non-specific protein, the reaction can apparently be transformed into an agglutination. It is possible to get a lessening of fertility in invertebrates without agglutination and without immobilization. This is illustrated also in the case of sea-urchins, in which there is a spontaneous reversal of agglutination.

Dr. Heidelberger pointed out that the main thing here is a reduction in the fertilizing power, whether or not there is agglutination. Dr. Tyler pointed out that this can be done without impairing sperm motility, in sea-urchins, for instance.

Dr. Szilard asked what heavy metal ions sperm were sensitive to, and Dr. Tyler said mercury, copper and zinc in low concentration will kill sperm. It may be possible to have a cumulative effect in high enough degree to kill the sperm. Dr. Reynolds pointed out the danger to the kidney in such a case. These metals are not expelled properly. Dr. Tyler stated that there is no question but that sperm are extremely sensitive to minute traces of heavy metal. This principle is actually used in some contraceptives. He pointed out that heavy metals might be administered in non-toxic form by the use of chelating agents. If then they were liberated from the chelating agent by the conditions in the genital tract or could be caused to dissociate only there, they would be available as spermicides. (Note that various chelating agents are used as antidotes in metal-poisoning.)

Dr. Bishop pointed out that there are relatively few sperm around a rabbit's egg, but experimenters diluted the rabbit semen to one in one thousand and still got maximum fertility.

Dr. Tyler had no information concerning lithospermum.

Dr. Davis then asked Dr. Tyler if fertilizin was a promising lead as far as this group is concerned. Dr. Tyler felt that it is a promising lead since it concerns the initial specific union of egg and sperm. Dr. Reynolds pointed out that insofar as the fertilizin-anti-fertilizin story is part of normal human physiology, it offers promise, but a lot of experimentation has to be done. Dr. Tyler pointed out that many different approaches are possible; the chemical composition of fertilizin, for instance, needs to be worked out. If some unique constituents were identified it might be possible to block the synthesis of fertilizin by methods of competitive inhibition. It might also be possible to get an organism to manufacture an excess of fertilizin so that it would be present in solution around the egg and block fertilization. These and other possibilities also apply to the anti-fertilizin of sperm. Dr. Tyler did mention that it will be quite a job, partly because of the fact that each step of experimentation depends upon the results of the preceding step. The procedure would have to be very general, in other words, basic research. With the exception of hyaluronidase there has been no survey in mammals of the compounds involved in sperm and egg interaction.. Tanabe, now at Penn State, as well as Dr. Bishop, were working on the general problem in Pasadena.

Dr. Reynolds suggested that a screening test similar to what the pharmaceutical houses do could be set up for effects on fertility, and asked

Dr. Tyler of what such a test could consist. Dr. Tyler said that ovarian ova from ripe follicles as well as ovulated ova could be used to test fertilizin. Follicular fluid, the uterine secretions, etc., should be examined in regard to their agglutinating and after effects on sperm. Knowledge of the natural substances might then permit some sort of screening test for effects of various related materials or substances on fertility.

Dr. Bishop suggested the possibility of producing antisera to cervical mucus.

Dr. Heidelberger said that mucins in general were not good antigens, but that adjuvants might be added. The contents of the mucus change radically with the cycle, also the proteins, so that optimum time is involved.

In answer to a question about phosphorylated hesperidin, Dr. Tyler said that he felt that there were a great many difficulties with this theory. For one thing, so-called Vitamin P is quite nebulous. There are many things that can go under this label; the concept is ill-defined. Also, the dependence of capillary fragility, or permeability on a hyaluronic acid-hyaluronidase system does not seem to be firmly established. He stated that one might accept the results of the Martin-Beiler work, but that the causal relationships are questionable. He did believe that the idea of blocking the hyaluronidase on the sperm was a good one. There are many possible inhibitors -- Pincus and Chang have made a study of some of them.

Dr. Szilard asked if these would act in high dilutions with local application. Dr. Tyler said that most hyaluronidase inhibitors require high concentration.

## Sperm Motility

Dr. Bishop noted that very little is known about sperm motility. A coordinated set of movements produces it, also uterine contractions. No one really knows what causes motility. Dr. Tyler stated that although fructose appears to have some relation to motility, that fructose is not necessary to have fertilizable sperm.

The egg probably moves by peristaltic action and possibly ciliary-fluid action of the tube. It takes the egg about four days to get through the short and convoluted tubes, going about half-way on the first day, and taking three days to get through the other half. Dr. Szilard suggested that a pharmaceutical product might influence the contractions, but Dr. Reynolds said the side effects of this might be too widespread, and it could result in tubal pregnancies.

Dr. Tyler pointed out that sperm have to be motile to be fertile, although the converse is not true. (i.e., sperm can be motile and not capable of fertilization. Motility does seem to have a part in the penetration of the uterine entrance or canal. Once the sperm hits the surface of the egg, it becomes motionless and the egg takes it in. Dr. Bishop pointed out that sperm should be capable of motility in the epididymis, and it is not known why they don't move. Dr. Reynolds asked whether, if there is something physiological here, you could investigate seminal vesicle fluid and use results to inhibit sperm motility. A fructose inhibitor, for instance, might be discovered in the fluid. Dr. Tyler pointed out that low oxygen tension may be important. Dr. Bishop indicated that it cuts down oxidation of phospholipids. However, it is likely that some other factor is involved although epididymal sperm do not become

motile if aerobic conditions are created. It is conceivable that there may be some glucose in the tube which could be utilized by the sperm under relatively anaerobic conditions and supply its low metabolic needs. However, demonstration of a sugar in the tubal fluid has been unsuccessful so far.

Dr. Davis asked if there were many people working on factors affecting sperm motility. Dr. Tyler said that there were not many, but Thaddeus Mann and Rothschild at Cambridge have been working on energy requirements of motile sperm. It has only been since 1949 that the biochemistry of smooth muscle has been worked on seriously. A mathematician, (physicist) Jeffrey Taylor, in Cambridge, has made a mechanical model of sperm, and there have been articles in the Proceedings of the Royal Society giving a mathematical account (sine waves of various magnitudes). This is not really very helpful except from a theoretical point of view.

Dr. Bishop pointed out that one thing to be followed up is the isolation of the specific protein of the sperm (the Russian work mentioned above). Spermasin is isolated from the whole sperm. It is a specific protein with enzymatic activities affecting ATP analagous to the action of actomysin. The first paper was published in 1935, but nothing is available here on the more recent work. A lot of enzyme systems and substrates in the metabolic system of sperm have been described by the British. There is no motility when ATP runs out.

Dr. Reynolds added that although "muscle" has been studied for years, it was only since 1949 that the fundamental biochemistry of smooth muscle has been investigated.

Dr. Reynolds stated that smooth muscle contains about one-half the

energy-rich phosphates which striated muscle contains. A drug or chemical reaction causing a decrease in concentration throughout the whole body will affect most those muscles containing the least phosphates -- (e.g., Smooth muscle of the uterus). There may be a parallel type of action in the case of epididymal sperm. For instance, a substance blocking energy from low concentration points might immobilize them. The muscle physiologists might make some contribution in this field.

## Tetrozolium Salts

Some work has been done on this by Svevag at Pennsylvania. It was tried as an indicator to color the sperm (when reduced it gives a brilliant red). It does not work well, however, because the sperm do not absorb enough. It was discovered quite accidentally that it inhibits sperm motility. If there is no glycolysis it will reversibly affect motility. (Under aerobic conditions sperm can utilize other things such as phospholipids; they do not need sugars.)

Dr. Bishop indicated that the level of toxicity of the tetrazolium salts is well above that necessary to immobilize sperm -- in the absence of a glycolysable sugar.

It was mentioned that testosterone will inhibit spermatogenesis, but there is a rebound after administration is stopped. (Sperm are produced at a higher level than before.) Hotchkiss at NYU, a urologist, would know about this.

Dr. Tyler asked Dr. Szilard about radiation as a means of affecting spermatogenesis. It seems that low doses stimulated it, but it has proved too dangerous a method to be used very widely. Müller has stated that there is great danger to the genes. Dr. Reynolds mentioned that radiation

will cause the testis to hypertrophy and become cystic sooner than it would otherwise.

Dr. Reynolds indicated the common confusion between fertility and virility and the importance of dispelling this confusion in making acceptable any male method of fertility control. Dr. Tyler agreed but mentioned that much evidence exists pointing to increase of virility with certain methods of reducing fertility.

Dr. Bishop mentioned that Henry Lardy at Wisconsin has worked on the regulation of sperm metabolism. Lardy feels that there is an entity in ejaculated sperm which is capable of altering the type of metabolism from epididymal to ejaculate type, and this entity has been (or can be) isolated from both sperm and semen. It may not be secreted, but it is there. Although it is not di-nitro-phenol it has some of the same characteristics. When added to epididymal sperm, this sperm metabolic regulator will alter the type of respiration. (The experiment has been done in vitro). This may present the possibility of a block. This, however, is important only in that we recognize it. Dr. Bishop did point out that, like in the question of motility, there is the possibility of inhibiting release of the necessary substance. He also cautioned that use of such an inhibitor might make it possible for epididymal sperm to live for many days in the female genital tract. Since epididymal sperm are capable of fertilization, such a procedure would hardly help in fertility control.

PROCEEDINGS

Friday, September 12, 1952

In Attendance: Dr. Kingsley Davis
Dr. Georgiana Seeger Jones
William Lourie
Dr. Samuel Reynolds
Dr. Leo Szilard

Dr. Jones stated that she and her colleagues have been interested primarily in a fungus which seems to inhibit sperm motility. The problem has proved difficult because nothing can be done as yet in vitro. The fungus grows well enough in a culture (a modified Sabourraud's) but there is trouble with drying. Also, it is hard to compare one sample with the next. Therefore, the work must still be done directly on patients. She pointed out that their conclusions must be taken with some reservations, because there have been only two cases for study. In both cases the existence of immotile sperm has been found in connection with a benign fungus, i.e., a man with motile sperm has a wife in whom the sperm in the cervical mucus are immobile. The fungus, however, does not grow in the cervical mucus, but in the vagina. The mechanical action of intercourse deposits it in the mucus. This fungus is definitely non-pathogenic. It is known to split urea, a fairly rare characteristic.

Dr. Jones and her workers have attempted to plant the fungus in the vagina. They have had no success in the case of one patient, a negress who had cervicitis, considerable discharge, and many leucocytes in the area -- the conditions therefore were not optimum. They had slightly better success in the case of another patient, a diabetic. Upon inoculating her and reculturing, they got back the culture. In answer to a question about the similarity of the two patients, Dr. Jones stated that both were between the ages of 25 and 30. (They routinely culture all infertile patients.)

They did find the fungus in one patient, a woman of 43, who uses contraceptives. She had had a period of sterility seven years earlier, but they did not know if she had the fungus at that time. There were no indications of bacteria causing sterility, but they have not studied this nearly so extensively as Buxton, for instance.

Dr. Szilard asked if these patients had normal vaginal flora; Dr. Jones answered there seemed to be predominating gram-negative bacilli. They don't know about the acidity and pH.

Dr. Reynolds pointed out that there are two possibilities here: 1) the existence of something in the body that supports the fungus and 2) something in other persons that kills the fungus (the existence in normal people of an antibiotic).

Dr. Jones said, in answer to Dr. Szilard's question, that the fungus was administered in large doses, either as a suppository with an agar base, or 2 cc. in a broth base, or with a cotton swab. They are planning to inoculate all post-operative patients.

They are not really certain that this fungus is spermicidal -- this is the main question. If they can get it to grow in women, this can be tested. It might be spermicidal in vivo, but until they can get the culture to grow in vivo, they can not test it, obviously. Dr. Szilard pointed out that the fungus need not be spermicidal, but there may be a low pH. Dr. Jones agreed and said that this is one reason for testing in humans -- it is difficult to get a good amount of cervical mucus. The acidity of the cervix has not been tested in connection with fungus.

The fungus is easy to kill with gentian violet. Both patients involved conceived after the fungus was destroyed. This, theoretically,

could be a lead since the fungus is both non-pathogenic and apparently easy to control.

The possibility was also considered that the bacterial flora might grow too rapidly for the fungus to get a chance to spread. However, Dr. Jones indicated that in the case where it took, it grew rapidly.

Dr. Reynolds asked if the animal husbandry people might have anything to contribute here. Dr. Jones said that they know so little about fungi, especially non-pathological types, that little can be done, but they are working on it. Dr. Szilard asked if there were any antibiotics used in the vagina, and Dr. Jones said that there were, the most common being triple-sulfa cream. Another is aureomyecin. Usually these are dispensed in creams or jellies. The main bacterial population is gram-negative normally.

Dr. Szilard pointed out that this looks like a good lead. It would be ideal if there is something which actually does grow in the vagina -- it might then be possible to develop better strains, more adapted to the vagina. The fungus grows prolifically in vitro, so the possibility is good.

Dr. Davis asked if it is known just what the specific action on the sperm is, and Dr. Jones answered that it might be competitive nutrition. Dr. Szilard asked how often it would have to be inoculated, and Dr. Jones thought it possible that once a year would be sufficient. A fungus that takes hold is very resistant.

Dr. Reynolds brought up the point that there might be repercussions on the male, as for instance, the occurrence of the fungus in the genital tract. It was agreed that this would not be so desirable on a mass basis -- although likely to be a rare occurrence.

In answer to Dr. Szilard's question on the time necessary to get results on this, Dr. Jones said that they had expected to progress faster than they had in fact done. The work might be done fairly quickly, however, even on humans. Although the use of primates is possible, human work is, of course, essential. Dr. Reynolds pointed out that when the work is known among gynecologists, for instance, there should be more rapid progress, because they would begin looking for the fungus in their patients.

It is believed that the problem of getting the fungus to grow in the vaginal tract can be solved.

## Penicillin By-Product

It was pointed out by Dr. Jones that Roy Hertz made the accidental discovery that some impurities of penicillin were spermicidal. This is the type of discovery that needs to be brought to light -- the people working on penicillin were eager to avoid such an effect, so that very little attention was paid to such a negative discovery -- was cast aside, so to speak. It was suggested that the yellow pigment penicillin impurity should be looked into. Hertz, at the National Cancer Institute, could be contacted.

## Endocrines

A great many women are amenorrheal, without having symptoms other than some hirsute growth; the condition can be corrected by giving small doses of cortisone, and this gives rise to ovulatory menorrhea. This response is very unusual in amenorrheal cases when the amenorrhea is cleared up. It is thought that this represents a specific adrenal defect, since the condition responds to cortisone.

The question arose as to whether amenorrhea is an active or passive occurrence caused by the presence or absence of a specific substance. Is estriol involved, and what does it do? It might have something to do with the hormone balance, and it might be possible to block degradation by the regular administration of an estriol pellet. Progesterone alone will sometimes cause menstruation, but not ovulation. With estrogens this effect is even more likely to occur. Cortisone will not do it, however. ACTH will suppress ovulation in small doses. It was mentioned that estriol is difficult to obtain because it hasn't been made on a commercial basis. It is unstable. Estriol pellets should be tried as a means of blocking ovarian estrogen on the degradation side. There is a lot of estriol in the system. Administration of it stops estradiol degradation and hence might affect ovulation through the pituitary; most people, however, do not think this is likely. Research is needed to determine empirically just what it does.

Pregnandiol would compete with estradiol without affecting the pituitary. This might be an ideal solution.

What is produced in the adrenal cortex and what is extracted from it may be different.

PROCEEDINGS

Monday, September 15, 1952

In Attendance: Kingsley Davis, William Lourie, Warren O. Nelson

Dr. Nelson said in answer to a question by Mr. Lourie that he thought that aminopterin is perhaps the best lead that has been discussed so far.

if it can be administered with more safety than it has in some cases in the past. He believes that phosphorylated hesperidin needs too frequent administration, and that it has too many potential side effects. He pointed out, for instance, that hyaluronidase is given to prevent kidney stones, and that phosphorylated hesperidin is an anti-hyaluronidase, so that it is not inconceivable that kidney stone formation might result from administration. This, of course, is hypothetical. No such effect seems to have been seen as yet.

Dr. Davis asked Dr. Nelson what his work had been, and he replied that they are working on factors affecting testicular function. They have been administering six androgen pellets (containing pure testosterone) of 75 milligrams each every six months to eunuchoidal men and to a series of feeble-minded men. The pellets are implanted in the back under the skin. Mr. Lourie asked if androgens can be modified so as to cause longer action, and Dr. Nelson replied that Upjohn claims that testosterone-cyclopentyl-proprionate, which has been given by injection every ten days, can be given once a month with success (150 mg.) (Upjohn's suggestion for use in eunuchoidal men.) Its effect is to depress the sperm count. There are apparently no harmful side effects.

Dr. Nelson did not know the cost of the pellets. He said that androgen is synthesized out of many substances, including soy beans, and that he does know that the price has dropped. The only occasions on which it has been used to prevent spermatogenesis were at institutes for the feeble-minded. He and Dr. Heller reported on such results in the Journal of Fertility and Sterility. Testicular biopsies showed that depression of the sperm count was the major apparent effect, but not the only effect. Fibrosis of the tubules occurred but disappeared when treatment was stopped.

In answer to a question as to how difficult it is to get cooperation from the directors of such institutions, he replied that it depends on the director. Dr. Heller worked through a resident physician at the institution in Oregon. The same sort of cooperation was received at Iowa, although here only females were subjected to hormone therapy.

Dr. Davis asked what difficulties were involved in the use of pellets to cut down fertility. Dr. Nelson said that there is the possibility of infection, and that occasionally the pellet is sloughed out as a result of such infection, or because of planting the pellet too close to the surface. Usually there is no discomfort reported. In answer to the question of whether absorption could take place through the skin if the androgen were applied in an ointment, he said that the amount would probably be too small to be effective. Dr. Davis said that pellet administration seemed to be rather a makeshift arrangement, and asked if there is any other way. Dr. Nelson said that this method did have the advantage of treating an individual only infrequently. He pointed out, however, that this method is still in the basic research stage and much more needs to be known.

In the case of treating male infertility, it takes about eight weeks to get the sperm count down to zero, and about six weeks before it starts back again (the "rebound"). The whole process takes about a year in some cases. Not very much is known about what is needed to suppress the sperm count of normally high-fertility men. There is a great deal of individual variation. It is easy to suppress spermatogenesis in animals. Not very much has been done with monkeys, especially in the field of male reproduction.

Mr. Lourie asked if much had been done on sperm maturation (with fura-

droxyl, or fructose, for example). Dr. Nelson felt that little had been done, probably because epididymal sperm are too immature. It has been shown conclusively that, in animals, the sperm in the head of the epididymis are much less motile and less fertile than those in the tail of the epididymis. (They are not motile within the epididymis.)

Mr. Lourie asked if the prostatic fluid can be altered to affect the motility of the sperm. Dr. Nelson thought that this might be a good possibility, but stated that this field is untouched. It is known that the epididymis is important and that male sex hormones are involved. (CF. physiological maturation vs. morphological maturation in epididymis.) This raised the question of the temperature of the testis and its importance in fertility. Dr. Nelson said that a $3^{0}$ - $4^{0}$ F. differential is necessary for maturation in animals which have scrotal sacs. However, malaria does not seem to have any permanent effects on fertility. Dr. Davis noted that high malarial areas generally have very high birth rates.

Dr. Davis asked what the mechanism is in the case of androgen administration. Dr. Nelson stated that the gonadotropins are affected. Although this area is not well known, it is true that sperm cannot go through the process of spermatogenesis without gonadotropins. How the gonadotropins work on sperm is not known.

Testosterone is manufactured in the testis. One of the degradation products which is excreted in the urine is dehydroandrosterone which is still a weak androgen. It will not compete with testosterone so far as is known, but possibilities exist in view of its androgenic nature.

Dr. Nelson said that his group did not investigate the action of large doses of androgen in stimulating spermatogenesis. In rats, guinea

pigs, mice and monkeys it is possible to stimulate spermatogenesis in the absence of the gonadotrophic hormones by giving large amounts of androgen. This has not been shown to be true for man. For a discussion of this "anomalous" effect of androgen see an article by Dr. Ludwig.

Dr. Nelson stated that he was satisfied that androgens do not cause prostatic cancer. However, if cancer of the prostate already exists, androgen therapy appears to exacerbate the condition. Prostatic cancer is very rare before the age of fifty and thus this complication is completely negligible in our problem of controlling fertility in under-developed areas.

Dr. Nelson's feeling was that we should not put too much reliance in the androgen method at the present time. He felt that lithospermum might be a better lead if it can be shown to have an anti-gonadotropic action. It probably would not need to be used continually, but could be given at the time of ovulation.

## Vasectomy

The question of vasectomy as a means of fertility control was brought up, and Dr. Nelson said that he felt that this, if accepted, would be the ideal solution. He did point out that the reversibility was an important factor, and that when one speaks of reversibility, one should distinguish between two possibilities, viz., the interruption of the vas deferens, somewhere along its course, and interruption of the connection between the vas deferens and the epididymis.

The first method is easily reversed although some failures must be expected even by the most competent surgeons. The second type of reanastomosis is much more difficult to achieve.

In cases where only the vas deferens is interrupted, spermatogenesis continues. (Also true if interruption of passage is between vas and epididymis.) Apparently the sperm eventually fragment and are phagocytized.

Dr. Davis felt that vasectomy offered a possibility for immediate field trial. Success might depend upon selling the idea that reversal was possible, but it was not thought likely that there would be much demand for reversal after the men discovered that virility was not impaired. Only males having at least three or four children would be considered for vasectomy. Pilot project might include skilled native surgeon plus a nurse or two to give general health assistance as well as this specific operation. They could, of course, offer birth-control advice to the women at the same time -- in cases when vasectomy of the males was not attempted. Dr. Nelson thought such a project might be feasible.

## Nitrofurans

Friedgood, at Maimonides Hospital, has been working on the effect of nitrofurans on human testicular cancer, and is the only one using nitrofurans on humans at present. The difficulty is that one cannot postpone operation long enough to test the results thoroughly. There have not been enough studies made on the nitrofurans as yet to know very much about them. Spermatogenesis in rats can be suppressed with the administration of furadroxyl without any apparent side effects. After treatment is stopped, there is evidence of recovery beginning after about three weeks, and another three weeks is required for complete recovery. In regard to the question of how long it takes to inhibit spermatogenesis after treatment starts, Dr. Nelson was not sure, but stated that Friedgood got results in eight days. We don't know yet if a single dose is sufficient. The most convenient way of administration is in the diet in animals, but it is

conceivable that pellets could be used. Solubility is so low that the effective amount is not yet determined. There are frequent cases of spontaneous azospermia*, with otherwise normal development. This leads to the hope that it will be possible to cause azospermia artificially without side effects.

The mode of action in male animals is apparently to cause spermatogenic arrest -- the primary spermatocyte never develops into the secondary spermatocyte. This experimental condition resembles certain cases of human spermatogenic arrest resulting from diseases with high temperature, occupations associated with high temperature environment, or defects in the pituitary. In humans, for the first two categories, the condition is temporary; after recovery from the disease or change of occupation spermatogenesis returns to normal. In the experimental animals, however, under nitrofuran therapy, there is evidence of a more toxic condition than in the human cases referred to -- that is, "toxic" to the meiotic division which the primary spermatocytes normally undergo.

In female animals, nitrofurans kill the fetus early. Mode of action is not known. It may be similar to that of aminopterin since implantation is not affected.

## Screening Tests

It was mentioned again that a battery of screening tests could easily be developed so that all compounds could be tested for reproductive effects. The Sloan-Kettering Institute tests a great many compounds for effect on cancer. It might be possible to use their experimental records as a start

*Note: The term "aspermia" usually means lack of seminal fluid. "Azospermia" is used to indicate lack of sperm in the seminal fluid.

on such a screening program since they apparently have made some observations on reproductive effects.

Dr. Nelson said that the effect of this conference and the Planned Parenthood Colloquium would be that he, and presumably others, would now have their attention focused on these problems of fertility control. He mentioned that among the South American laboratory people capable of working in this field, were Bernardo Houssay in Buenos Aires, Thales Martin now in Rio de Janeiro, Alex Lipschitz in Santiago and Filipe de la Balze in Sao Paolo.

TRAIN, Percy, J. R. Henrichs and W. A. Archer, "Medicinal Uses of Plants by Indian Tribes of Nevada" Part II, 1941. The Division of Plant Exploration and Introduction, Bureau of Plant Industry, U. S. Department of Agriculture, Washington, D. C.

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LITHOSPERMUM RUDERALE Dougl. Boraginaceae

(S) nem-ish-aw; nom-ish-aw. (E) gromwell, stoneseed.

Among most of the Shoshones the root of the plant is a favorite remedy for diarrhea. For this purpose the root may be boiled or soaked in water. The potion is considered to be especially helpful in stopping bloody diarrhea.

In one settlement it is believed that the plant has contraceptive properties (Osyhee - S). It is said that the cold water infusion from the roots, taken daily as a drink for a period of six months, will insure sterility thereafter.

PROCEEDINGS

Wednesday, September 17, 1952.

In Attendance: Kingsley Davis, Jules Freund, Paul S. Henshaw, William I. Lourie, John MacLeod, Theodore T. Puck, Samuel Reynolds, Robert G. Snider, Leo Szilard

Dr. MacLeod outlined to the group the work he had been doing and the circumstances under which it had started and been continued. He had been interested in the broad problem of what constitutes male sterility. In the beginning, the approach was fairly broad, but there was increasing pressure to devote time to practical problems and, as the work progressed, this was done. The problem he has been investigating is the metabolism of sperm, i.e., the enzymes responsible for motility, the necessary substrates, inhibitors in the enzyme systems, etc. In this way, he has been able to get at the key enzyme systems.

His laboratory has been acting as a diagnostic laboratory for fertility and sterility for Cornell Medical Center. As the data grew, the problem became obvious and separate studies were undertaken on the side. One of the first groups to be studied as such was what Dr. MacLeod called a "normal population", i.e., married males, having legitimate offspring, with the circumstances of conception known. They have also studied a group of medical students and a group of infertile males.

One of the discoveries which Dr. MacLeod has made is that past standards of fertility had been much too high. A count of sixty million sperm per cc. of semen had been considered normal, and he felt that it should now be realized that this is too high. Factors such as the effect of continence and frequency of emission must be considered in analyzing sperm count. Dr. MacLeod said that his work had shown that frequency

of intercourse has a great deal to do with ease of conception and, contrary to the opinion often expressed, more frequent intercourse increases the likelihood of conception, i.e., intercourse four times a week led to conception more frequently than intercourse twice a week. Sperm count, sperm motility and the morphology of the cells, were analyzed in terms of frequency of intercourse, the time of the last emission, and age. There is no appreciable change in the quality of sperm up to the age of about forty-five. Eventually, he hopes to have data concerning older males.

Dr. Henshaw brought up the fact that Farris felt that too-frequent intercourse led to sterility, but Dr. MacLeod disagreed with this conclusion.

Dr. MacLeod stated that there is no relation between sperm count and fertility above a certain level. Twenty million per cc. is the rough dividing line. The important thing is the quality; a low count can be compensated for with good motility. The motility is related to the time necessary for conception.

So far, sperm morphology does not seem to be related to anything. Dr. MacLeod pointed out, however, that this may be due to unsatisfactory criteria, which may be modified. Dr. MacLeod stated that he knew of no relation between morphology and miscarriage, but it was pointed out that this theory did occur in the literature.

Dr. Henshaw asked whether motility was an important point to be considered in any attempt to modify fertility, and Dr. MacLeod said that it was. He stressed, however, that all inhibitors affecting the carbohydrate enzyme systems are general poisons. The sulphydril group presents very important possibilities. A method employing small amounts

of copper (a few gammas per cc.) is another possibility. It would not be feasible to put such a poison in the vagina, however. Any possible method must be in terms of the whole physiologic process of fertility, which, Dr. MacLeod stated, we don't know too much about, at least insofar as what actually happens between egg and sperm. One of the unexplained phenomena, for instance, is the fact that sperm have relatively poor motility at the time of ejaculation. They are mechanically immobilized by the medium, and rapid liquefaction is needed for the necessary increase of motility. He does not believe fructose to be a major factor. Although the process of sperm transport is not fully understood, Dr. MacLeod believes that it must be a physical or migratory process. A clot of sperm is immobilized for quite a little while in the fornix. Dr. MacLeod postulated that a sort of forceful pushing of the sperm into the cervical canal might be one explanation of the apparent link between minimum sperm count and fertility.

Dr. Szillard asked if it were possible that the uterus might aspirate the sperm. Dr. MacLeod thought this unlikely.

In regard to the role of fructose, Dr. MacLeod thought this sugar unimportant and probably overrated. Rather than the concentrations of fructose in uterine secretions, he viewed the glycogen content as of greater significance. Glycogen upon diastatic breakdown yields glucose -- a more important metabolite for the sperm than fructose.

In relation to the question of average time needed for conception in the so-called "normal" population, Dr. MacLeod stated that it was about four months (for the couple's most recent child). This may be due mainly to the frequency of intercourse in younger married couples -- three or four times a week. There is also the fact that for women conceiving

very early in the marriage, the frequency of intercourse is even higher. In other words, high frequency of intercourse may be the main explanation for the high pregnancy rate in the early years of marriage. On the other hand, early conception may indicate a high fertility to begin with, so that the 4-month average time for conception referred to above must be considered with this reservation in mind. The age of the wife has turned out to be very important, but, even in older women, frequency of intercourse remains an important factor.

As regards the relationship between semen quality and conception, it has been found that sperm with a high grade of motility, i.e., rapid movement, cause conception most easily, the ratio being 2.2 months for these as compared with 8 months for sperm of low motility. Quality of motility is gauged in terms of direction of movement, speed of movement, and percentage of active sperm. Sperm quality is measured by an arbitrary rating according to a 4-3-2-1 scale, which permits close grading by using + and - intergradations.

Dr. Davis asked why the percentage of motile sperm is important. In the discussion that followed, it was pointed out that in the case of bulls, with fractionated ejaculate having a total count of twelve million or more, there is no rise in fertility potential. Further, the number of conceptions doesn't fall off much down to a count of two million. In the case of humans, however, the absolute number of cells has some importance. With a count of twenty million, an active group of 40% is required in terms of quality (when the sperm have a motility of 2+). Dr. MacLeod mentioned that this was based on his own observations.

Dr. Reynolds asked how long specimens could be kept and Dr. MacLeod stated that they could be kept up until seven or eight hours, but there

is not much variation once liquefaction takes place until six hours has elapsed. Specimens were kept at room temperature, but he noted that the relation of temperature to motility is not very significant. The temperature coefficient is physical rather than biological. The laboratory did not accept a motility reading after about five and one half hours.

In humans, frequent intercourse decreases the number of sperm per ejaculate, but not necessarily their fertility. The sperm in the ductus deferens are the important ones as far as the ejaculate is concerned. The sperm from the epididymis are morphologically mature by the time they are ejaculated.

Dr. Freund asked about the source of the enzyme hyaluronidase. Dr. MacLeod said that it came from the testis or germinal epithelium, not the prostate. Dr. Freund said that it is in the head of the sperm. Dr. MacLeod indicated that hyaluronidase may be absorbed on to the surface of the sperm. He felt, however, that hyaluronidase had little if any relation to fertility.

Dr. Henshaw asked about sperm ripening, and Dr. MacLeod said he had no direct experience with humans, but from Chang's work it appears that there is some maturation in the female genital tract.

Dr. MacLeod stated that the ages 20 to 25 were the most fertile period in the female, and that after that there is a definite drop. Dr. Davis pointed out that this is confirmed by demographic data, even though the role of the male is not defined in such data.

Dr. Henshaw asked if there were many <u>in vitro</u> studies of sperm-ova fertilization. Dr. MacLeod said that there were not and that Dr. Rock in Boston was the only one to have had any success with this; it was then noted that Rock is somewhat dubious now about the interpretation of his experiment of five years ago.

Dr. Henshaw referred to the possibility of building up an ovary bank. Dr. MacLeod informed the group of the work done by the Parkes Laboratory in England in preserving sperm for six months, but he did not know of any success in preserving ova. Dr. Reynolds said that Parkes' results had been given in a paper at Edinburgh before the British Association for the Advancement of Science.

In answer to the question of a reversible radiation method, Dr. MacLeod stated that he knew of none except diathermy. The objection to x-ray is the difficulty in properly grading the dosages. The objection to x-ray from the point of view of genetics was also mentioned. Dr. MacLeod felt that W. C. Young of the University of Kansas, Lawrence, Kansas, would be likely to know about the effects of radiation. Frank Dixon, Department of Pathology of the University of Pittsburgh has written a monograph on the subject of the effect of x-ray on the testis. Dr. Henshaw also referred to Bloom at the University of Chicago.

## Diathermy

One or one and a half hours of diathermy to the testis will inhibit spermatogenesis for three months. However, since the germinal epithelium, and not the sperm, is affected, it takes about three weeks for mature sperm to disappear. The same is true of other methods affecting germinal epithelium. Dr. MacLeod saw little danger of permanent effects from diathermy.

## Dr. Freund's Work

Dr. Freund described his and his associates' (M.M.Lipton and G.E.Thompson) experiments, which, in brief, were as follows:
a few hundred thousand guinea pig sperm were taken, mixed with paraffin

oil containing acid-fast bacilli, and injected into the skin of the guinea pig. In three or four weeks, there were no spermatozoa and practically no spermatogenic cells. The effects last six months or longer and with a booster injection, it would probably last two or three years. Sperm alone may be sufficient for the booster injection. The interstitial cells and Leidig cells are untouched but the Sertoli cells may disappear. Sperm from the same guinea pig can be used, or from the same species. These were washed, unfractionated sperm. Sperm may be replaced by a suspension of testis or mitochondria-like preparation from the testis. There is no inflammation of the testis, but later on there may be an excess of connective tissue and fibrosis of the seminiferous tubules, although not necessarily. After six or seven months, this treatment may be reversible, but Dr. Freund stated that they kept the guinea pigs only seven months so that they do not know the long-term effects. He suspects that reversibility is possible. There is no anaphylactic shock upon second injection.

Dr. Freund then showed the group some slides showing parts of the testis and epididymis. In relation to the question of restoration after treatment, Dr. MacLeod pointed out that you cannot expect regeneration once the spermatogonia are destroyed. Dr. Freund pointed out that in some cases, if you inject sperm alone, the spermatogonia last longer or do not disappear. Dr. Reynolds asked what happens when you inject paraffin oil and bacteria alone. Dr. Freund said that with the same size injection nothing happens. If these are injected into the testis or peritoneal cavity, there is inflammation or atrophy. If the injection of sperm and adjuvant is into the female, she produces antibodies against the sperm. Dr. Reynolds asked about the number of pregnancies that occur afterward, and Dr. Freund said that six out of ten became pregnant, but

it was a poor experiment so that he would not want to state the results with assurance. The potency of treated males was not studied, but theoretically it is still unaffected because the Leidig cells are not affected.

Dr. MacLeod asked what led to the use of this method. Dr. Freund said that it was believed that brain, cord and testis had an antigen in common, but experiments disproved this theory and the injection of central nervous tissue with paraffin oil and killed mycobacteria produces sterike allergic-encepho-myelitis.

Dr. Fruend stated that some females were also injected, with a suspension of ovaries. Those so treated appeared to be normal.

Dr. Reynolds pointed out that Drs. Heidelberger and Bishop had implied that Dr. Freund's work was an extension of their own. Although doubting that Dr. Heidelberger or Dr. Bishop had said that Dr. Freund stated that it was in a sense, but that his experiments were new. If you inject sperm (any kind) into rabbits, antibodies will be formed, but the testes of such animals are normal because no adjuvants were used. With adjuvants, however, there is danger of permanent damage in the male. The spermatogonia may eventually be affected. A great deal depends on the dost, which is yet to be investigated in detail.

Dr. Freund mentioned that a French paper by Voisin et al (Annal. Inst. Pasteur 1951 or 1952) had discussed the injection of testis or kidney or liver suspension with adjuvants. They found that their animals either died or became ematiated. The effect on the testis was interpreted as nonspecific stress-effect. Their observations and conclusions are at variance with those of Dr. Freund and his associates.

Dr. Szilard asked if they plan to do any work on the female,

but Dr. Freund said that they do not at this time.

In relation to the question of how long the immunity lasts, Mr. Snider pointed out that if it is seven months in the case of the guinea pig, the comparable span in humans may be much longer.

Dr. Freund stated that the animals tested do not lose weight, and go on growing. Histological sections of all organs (brain, liver, kidney, spleen) show no change. Dr. Reynolds asked if the reaction was specific to the testis, and Dr. Freund said it was. Sperm alone cause no change after five or six injections. When you compare the antibody formation caused by sperm in oil with that caused by sperm in salt solution, the difference is in favor of the former. When bacteria are added, there is a further enhancement in antibody formation and aspermatogenisis probably allergic in nature.

When tubercle bacilli are used there is a reaction at the site of injection, a nodule which may suppurate. There is no infection, however. It is possible to use a dead fungus, which is just as effective as tubercle bacilli (Nocarolia asteroides).

As far as local reactions are concerned, it was pointed out that such reactions might be all right in India, but not in the United States.

Dr. Szilard asked if the use of adjuvants raised antigen titre in females high enough to stop fertilization, and Dr. Freund said he would expect higher titre, but had no data on the effectiveness of the titre for such purposes.

It was stated that we know very little about the presence of antibodies in the reproductive secretions. Dr. Reynolds mentioned that in monkeys, the amount of fluid secretion is related to the rate of blood flow.

## Dr. MacLeod's Laboratory Organization

Dr. MacLeod has been working with just three people; himself, a statistician, and a technician. They have three rooms, the laboratory being about 412 square feet. One of the smaller rooms serves as his office. It has taken several years to set up the equipment at a total cost of about $10,000. He has done nearly everything himself. He pointed out that the hospital histories will not be sufficient for their purposes, and they kept their own records, adding to the material furnished by the hospital. They had a grant of $6,000 for the first year (1949) and their 1952 budget has been between $10,000-$15,000. Dr. MacLeod felt that they had had more than enough money for their needs, and could have gotten along with less, in fact. He thought the whole program could be run on $8,000-$9,000 a year. Scientific motivation has, of course, played a large part in their work. The right type of graduate student would have helped; usually medical students have too full a program. His teaching duties have, of course, slowed down his progress somewhat. Since the beginning of the program, Dr. MacLeod estimated that he had spent about $80,000.

Dr. Davis asked about the production of articles and Dr. MacLeod said that he is now working on the eighth paper of the series. They have averaged about four papers a year, and are aiming at a monograph. Dr. MacLeod stated that about three years were necessary to do the statistical part of their work, and that much of what has been done so far is the laying down of standards of fertility. He expressed a desire to be able to get back to more fundamental considerations and said that in work of this kind, keeping up with the field and not getting immersed in the more routine parts of the work is an important consideration.

They have three or four thousand marital histories in detail, including the wife's history and abnormal conditions. Follow-up is an important part of the work.

Dr. Henshaw pointed out that in many of the situations he had encountered in his interviews, there was a great deal of emphasis on special problems and no opportunity to follow up and put conclusions together. Dr. MacLeod said this is exactly what he had tried to do, namely, start with the males, bring the females into the study, and thereby get the complete picture.

Dr. Henshaw asked about his experience with androgen, and Dr. MacLeod said that he was sorry that he hadn't been able to confirm Heckel's work on the rebound phenomenon. He has been using about 35mg. of methyl-testosterone per day until azospermia appears. Recovery was to the same level, not an increased one. There were no side effects, no increase in libido, no exaggeration of secondary sex characteristics; these points, however, have not been investigated very thoroughly. One man went for five or six months without a decreased sperm count. Dr. MacLeod also pointed out that he had one case of a testosterone addict; the man came to a clinician because he noted a decrease in potency, and was put on androgen. He was satisfied with the results in relation to potency, but the treatment resulted in his becoming sterile. He would not be taken off testosterone, even in order to have children. Placebos were ineffective. He had been referred by a psychiatrist.

Dr. MacLeod said, however, that he would hesitate to publish anything in reference to Heckel's work; Heckel waited fourteen months for the rebound in some cases, and Dr. MacLeod felt that this was a long-period.

Dr. MacLeod expressed the opinion that infertility in males is an inherent phenomenon, and not an accident of adult life. Sometimes the semen is better at the age of 45 than at a younger age. The sperm picture is as constant as fingerprints.

Dr. Sieve's work was outlined to Dr. MacLeod and he expressed interest in this type of work. He did feel that the failure to conceive was not a sufficient criterion of infertility.

## Immunization

Dr. Freund pointed out that when you immunize guinea pigs with sperm you get three kinds of antibodies in sera --complement fixing, immobilizing, and anti-hyaluronidase. It is not unlikely that the circulating antibody is higher in titre in the female because the testis may absorb some of the antibodies. Otherwise, there is no difference as between male and female. The sperm could be fractionated. Some people have claimed that there are agglutinins. It is difficult to make a test of this. The antigen in the head of the sperm is different from that in the tail. Complement is not necessary for agglutination but is necessary for immobilization.

Reference was made to the Hertz experiment in which penicillin in its impure form caused immobility of sperm in vitro.

Any lead that cuts down motility looks good. Dr. MacLeod feels that this is very important because motility is very sensitive.

Dr. Freund feels that it is a mistake to assume that hyaluronidase has no effect on fertility. There is another antibody in his experimental animals, namely antibody against hyaluronidase.

The situation is similar to allergic encephalitis. If you inject brain or cord alone in a saline solution several times, there is no

change in the central nervous system; with the addition of killed mycobacteria in oil you get symptoms and morphological changes. It does not appear that there are serum antibodies involved. Animals are hypersensitive to brain or cord in the skin. Sensitivity created this way cannot be transferred to another animal as in cases of anaphylaxis.

Dr. Davis asked if anyone else is doing work and Dr. Freund said that no one is. It was suggested that Dr. Gertrude Van Wagenen at Yale might do it on monkeys. One laboratory is doing polio work on immature monkeys.

It was pointed out that fractionated material mitochondria from the testis is just as effective as whole testis or whole sperm. It was suggested again that an institution for the feebleminded would be a good place to test this.

Once sensitivity is established, the second injection need contain only the original antigen.

Dr. Freund does not look with favor on Wharton's jelly. It contains a lot of hyaluronic acid. No one has succeeded as yet in using this acid with adjuvants. It was suggested that Paul Weiss at Chicago might know the effect of the other contents of Wharton's jelly.

Ebert has done four papers on the effect of antibodies on embryos.

In answer to the question of whether the embryonic cord contains any substance that could be used, it was pointed out that Lumsden and Kabat at P & S have done some work on this. It was reported in the Journal of Experimental Medicine. They injected monkeys with monkey brain and found antibodies. They then took the placenta to test sera. However, it turned out to be a matter of blood vessels, which is not so important for us. Dr. Reynolds pointed out that the placenta has fragments that

break off and get into the bloodstream when they are phagocytized. Such fragments cause no immune response.

One man has claimed that by injecting blood serum from chickens as a test for immobilizing sperm, he got antibodies against sperm at the time of sexual maturity. Dr. Reynolds pointed out that sensitivity depends somewhat on the endocrine balance. In some cases where animals were pregnant, the uterus could not be sensitized.

PROCEEDINGS

Thursday, September 18, 1952

In Attendance:

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| Dr. Kingsley Davis | Dr. Samuel Reynolds |
| Dr. Earl Engle | Mr. Robert Snider |
| Dr. Paul S. Henshaw | Dr. Leo Szilard |
| Mr. William I. Lourie | Dr. Howard Taylor |

Dr. Reynolds summarized briefly the work that Dr. Jones had reported and asked Dr. Engle about the work that Dr. Buxton had been doing at the College of Physicians and Surgeons. Dr. Engle said that Dr. Buxton had found two kinds of bacteria that immobilize sperm in vitro almost immediately. They come from the cervical mucus of women with a considerable history of sterility. They immobilize sperm very quickly. Dead bacteria do not do it. However, there seems to be little possibility for fertility control here, since 51% of all women carry these organisms.

Dr. Reynolds asked about the kind of organization needed to achieve our ends, and Dr. Engle stated that any organization represents a capital investment, and it's hard to stop even after a mistake has been made. The cheapest way would be to use already existing research facilities. A lot of people in established institutes would be interested in the kind of work which we wish done. A general research program on an annual subsidy basis would be better than contract work. Research organizations could act as stand-by organizations on a maintenance basis.

Dr. Reynolds pointed out that the methods for doing research in this country are pretty well defined, and it is wiser to proceed according to established methods of procedure.

It was pointed out that the Committee on Human Reproduction has now been dissolved. Dr. Taylor stated that it operated effectively for only about a year. The Committee had been authorized to announce in Science

a fund of $100,000, and $200,000 for the following year, but then the funds were not available. The problem was that of support, not of ideas. From the beginning the objectives were not too well agreed upon. The supporters were interested in practical results, and the members of the committee in basic research. It was noted that the same type of thing happened in cancer research, but the scientists have, in a sense, won their objective, because they are still doing basic research and a cure has not been found.

It was pointed out that a compromise is needed here; the supporters must realize that basic research has to be done, and the scientists must accept the need for solutions. Timing of such a balanced program is probably better now than when the Committee started.

Dr. Davis asked if, on the basis of the past experience of the Committee, the present time is a good one to undertake a new program. Drs. Taylor and Engle felt that the past difficulties may have lain with certain individuals and not with the program. They did feel, however, that the medical profession as a whole had become somewhat disenchanted, and that there might be resistance to a new program unless it differed widely from previous ones. It was noted that our problem is basically easier than that of the cancer researchers.

Dr. Engle is not in favor of modifying fertility physiologically. He feels that the side effects are potentially great and very dangerous. The group agreed that systematic screening of chemical substances, intended to suppress ovulation or implantation, would be a good thing, if it could be done without discouraging original research. Dr. Engle felt that we might do well to look for very imaginative workers, even those less practical, because what is needed here is something very revolutionary.

Dr. Taylor reported that in Puerto Rico and elsewhere, there is a

practice of sterilization on the third post-partum day. Then the muscles are relaxed, yet the uterus is still enlarged. The patient's return home is not delayed, and it is a simple operation.

Cauterization of the uterine horn in non-pregnant patients is also possible. Dr. Norman in North Carolina has worked on this, and is planning to come up to P & S to demonstrate it. It is a simplification of an operation Dickinson described and possibly performed. Actually it is not really an operation, the instrument being introduced by way of the cervix.

(Dr. Reynolds asked if anything had been done in the husbandry field, and although he felt that nothing had, Dr. Engle pointed out that this would be a very valuable development, because breeders would not have to segregate animals too young to breed.)

(Puerto Rico operation.) This operation has been done in the last ten years. It is supposedly required that this is done only for women who already have five children. Dr. Taylor pointed out that women are most susceptible to the influence of physicians at the time of delivery; this is important, because the spread of birth limitation requires education. This operation is safe, private, and performed in a single step. Any country with a reasonable percentage of hospital deliveries could utilize this method, but hospital deliveries are not common in places like India.

Dr. Davis pointed out that in Japan abortion is preferred to contraception. There are 600,000 officially recorded abortions plus probably many unrecorded. He thought it might be possible that the Japanese would accept sterilization as an alternative to abortion if presented to them properly.

## Male Sterilization

Dr. Engle brought up the possibility of male sterilization by non-surgical means. Aspermia does not impair endocrine function. The greatest problem is the psychological one. The possibility of selective radiation affecting the germ cells was discussed with suggested radioactive labelling of the arginine in the sperm head to eliminate spermatogenesis. This would be selective for sperm alone. Arginine storage in the liver, however, might lead to side effects. However, any method based upon the sulphydril grouping was thought to be worthy of investigation.

## X-Ray

Dr. Szilard asked what radiologists would know about the effect of various x-ray dosages, and Cantrell at Oregon was suggested, also the Oak Ridge people. Dr. Davis pointed out that the theoretical work goes only so far, and such a procedure would have to be tried out in a village.

The genetic objection has been raised several times, but the experience of the Hiroshima people causes one to doubt this objection. Dr. Engle said that so far as he knew, the surviving males affected by the atomic bomb either became sterile or else regained their fertility within two to three years. There has, of course, been no opportunity to test subsequent generations.

Mr. Lourie asked about the nitrofurans, and Dr. Engle said they were toxic and would cause much trouble in the tubules.

As to testosterone, the administration has been with unreasonably large doses. Dr. Engle mentioned that the possibility of prostate cancer with the use of testosterone has not yet been disproved.

Dr. Szilard mentioned the idea of cauterization on one side (i.e. one

tube). It was pointed out that this may be ineffectual because of the internal migration of the egg to the open opposite tube. Sperm also could migrate to the ovary on the side not cauterized.

Dr. Reynolds brought up what he considered a very unlikely idea, but one which raises a point which should be investigated; that is, the occurrence of endometriosis. In this disease, bits of the endometrium get separated, travel elsewhere in the body, and continue their function of monthly bleeding from their new location. It is a disease which seems to occur in fairly young women who have postponed childbearing, i.e., it is associated with infertility. Scott at Western Reserve has worked on this and produced endometriosis in monkeys by blowing $CO_2$ into the uterus at the time of menstruation. It should at least be determined which comes first, the sterility or the endometriosis. Dr. Taylor reminded the group that endometriosis is a pathological condition and productive of much pain.

It was pointed out that a research staff of perhaps only two men should be put on the question of cauterization. The work could be done in institutions for the feeble-minded. The tubes and uteri could be examined three or four weeks after cauterization to determine the effectiveness of the treatment.

Dr. Davis asked Dr. Taylor about aminopterin. The latter pointed out that in this country, at least, there is a distinct difference between abortion and contraception in people's minds. An attack on the placenta, from a physiological but not from a theological viewpoint, implies less than an attack on the ovaries or the pituitary. The technical point can be made that if you give a potential abortifacient at the time of menstruation, then you never know for a fact whether or not pregnancy occurred, therefore there is not really an abortion. He believes that there is a

good chance of finding something specific against the trophoblast for instance, since the placental tissue is highly specific. Japan, which has a high abortion rate anyway might be a good place to try out something like this.

Dr. Reynolds also mentioned the administration of micro-crystals in an aqueous solution, injected intramuscularly. The crystals are absorbed and not sloughed off.

Dr. Szilard pointed out that good toxicity tests need to be made. They are usually done on four subprimate species (not monkeys--they are too expensive). It was agreed that animal research should be done, testing all sorts of allied compounds.

Dr. Reynolds mentioned that ovulation in women can be observed with the use of culdoscopy. By noting a drop in temperature, the time of ovulation can be predicted within 48 hours. The culdoscopy technique is as follows: a $CO_2$ trochar is inserted through the vaginal wall; $CO_2$ is blown in to push away the intestine; the trochar is removed and the culdoscope inserted. The uterus and ovary appear to be suspended, and ovulation can then be observed. Five such culdoscopies can be made in about 2 hours.

Dr. Taylor felt that the Puerto Ricans could probably be interested in the cauterization procedure. Such an operation could be done with technicians in a place like India, with antibiotic therapy at the same time. Dr. Taylor did bring up the point that this technique has been known for fifteen to twenty years, and one might be suspicious as to why it has not been utilized more widely if it is satisfactory. It was also pointed out that the technicians would have to be well-trained. If the electro-cautery were applied too long, it could perforate the uterus.

Dr. Taylor pointed out that there is a technique sometimes called

chemical hysterectomy. Zinc chloride is used on the lining of the uterus; it stops menstruation by destroying the endometrium. It is sufficiently thick so that it does not run out into the tubes. A complete job would stop menstruation, but it would be possible to leave enough of the endometrium to maintain menstruation yet prevent implantation. There is no pain, because there are very few nerve endings in the uterus. The dangers of infection would have to be avoided, as well as transporting the chemical into the pertoneal cavity. Here again, research on the feeble-minded might be done.

It was thought that this process of using zinc chloride could be used for cauterization of the tubes. Dr. Taylor pointed out that a very clever instrument maker would be needed. About two years testing time would be needed.

The concept of bacterial causation of infertility has gained great scope recently. It has not been proved, however. Dr. Henshaw pointed out that Buxton would be very interested in working on this. He already has a Public Health Service grant, the facilities, and the background.

PROCEEDINGS

Friday, September 19, 1952

In Attendance:

Dr. Kingsley Davis
Dr. William vE. Doering
Dr. Caryl Haskins
Dr. Paul S. Henshaw
Mr. William I. Lourie, Jr.
Mr. George Merck
Dr. Samuel Reynolds
Mr. Robert G. Snider
Dr. Leo Szilard

The first question asked of Mr. Merck concerned the advisability of having a special agency for the screening of compounds with respect to effects on fertility. Mr. Merck responded that the Merck Company would be very happy if it could get such work done outside its own plants. It would, moreover, be willing to pay for such screening of its products.

Dr. Szilard discussed a type of coordinating research program adopted at the University of Chicago, M.I.T. and California Institute of Technology, whereby industrial firms as sustaining members financially support a research organization for study of a specific scientific field. He wondered whether such an organization might be established to develop methods of fertility control. Mr. Merck said he was not optimistic. This pattern of research support had already been used and perhaps overworked. A program of research in fertility control would probably require a new and original pattern of support.

Mr. Merck reacted favorably when told that results of our proposed research program would aid childless couples in overcoming infertility as well as enable fertile couples to have a family of a size which suits their economic means. Research toward alleviating childlessness, in Mr. Merck's opinion, should be emphasized. Such research would be the best first step in the United States toward acceptance by manufacturers of an important role in a general fertility control research program.

In regard to developing and selling a specific compound, Mr. Merck indicated that often there is a great need for competition in the field. The problem of educating the medical profession and the public concerning the uses, actions, and desirability of a particular chemical is often too great to be borne by one company alone. On the other hand, if too many firms enter the same field, very few make any money. As an example, he mentioned that the government interest in antibiotics had caused so many companies to expand in this area that many of them were losing money on this part of their operations.

For effective clinical testing of a compound, the material must be made available on a large scale. Manufacturers set up "pilot plants" for this purpose. However, such a program carries the danger of over-advertising which creates such demand for the product that the company is swamped with orders before it is ready for volume production. Mr. Merck suggested that we would have to beware of this possibility when new methods for fertility control are developed to the testing stage.

The question was raised of the advisability of holding discussions, colloquia, symposia, etc., with representatives from industry to acquaint them with the urgency of the population problem and of the need for research in fertility control. Mr. Merck agreed that such discussions might be of great value in stimulating the necessary research. He felt, however, that success would depend upon the reputation and scientific acceptability of the organization sponsoring any such meeting. Highly respected groups such as the National Research Council or the American Academy of Science represent the type of organization he thought should originate discussions of this nature. He stressed the importance of inviting industrial scientists as individuals not as representatives of specific firms. The best people

to get, he stated, would be those aggressively interested, not those who had to be high-pressured to take up such a project.

In presenting the problem to the industrial scientists, Mr. Merck suggested that the best approach is just to tell them the facts. No attempt should be made to slant the discussion in terms of possible profits, greater markets, or other conceptions of industrial motivation.

He suggested contacting Frank Howard and Joe Barker concerning possible relationships between academic research and industrial research. Chauncey Leek of the University of Texas was also mentioned as a valuable contact. During the discussion, Mr. Merck emphasized the point that any research allocation to universities should be dispensed geographically. The Far West, in particular, should not be overlooked.

The group discussed the selection of men to lead research programs. Mr. Merck stated that attempts should be made to obtain men with well-established scientific reputations as research directors. However, he would justify the selection of relatively unknown scientists with adequate training and experience if they were especially interested in the program. However, if positive research results were achieved, those obtained by a staff headed by a well-known man of scientific repute would receive immediate acceptance, whereas results obtained by an unknown scientist might have to wait for confirmation before the results were generally accepted.

Mr. Merck stated that we have to show industry how to work in this field without bearing a heavy load. Many companies will wish to enter the field to at least a small extent, for fear of being left out of any future developments.

The question was posed as to the difficulty of interesting in fertility research the foreign subsidiaries of American companies. It was

felt that methods might be accepted more readily in underdeveloped areas if it were known that the technical work was not done in the United States. Mr. Merck replied that the major problem was that of interesting the parent company in fertility research. Once the parent company has made the decision, it is a very simple matter for them to direct the subsidiary to work on the project.

The group was encouraged by the discussion with Mr. Merck, since it made clear that industrial cooperation was very probable once industry had been acquainted with the urgency and nature of the problem. In addition, Mr. Merck's favorable attitude toward an independent screening laboratory emphasized one possible method of interaction with pharmaceutical companies to speed progress in the field.

APPENDIX NUMBER THREE

Working Group of the Conservation Foundation, September, 1952-March 1953:

Kingsley Davis, Professor of Sociology, Columbia University
William vE. Doering, Professor of Chemistry, Yale University
Clair E. Folsome, M.D., Director of Department of Obstetrics and Gynecology, Flower Fifth Avenue Hospital, New York
Alan F. Guttmacher, M.D., Director of Department of Obstetrics and Gynecology, Mt. Sinai Hospital, New York
Caryl P. Haskins, President, Haskins Laboratories, New York
Paul S. Henshaw, Director of Research, Planned Parenthood Federation
Frederick L. Hisaw, Professor of Zoology, Harvard University
Evelyn Hutchinson, Professor of Biology, Yale University
Samuel R. M. Reynolds, Carnegie Embryological Laboratories, Baltimore
Robert G. Snider, Vice President and Director of Research, The Conservation Foundation, New York
Leo Szilard, Professor of Biophysics, University of Chicago
Howard Taylor, M.D., Professor of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University

Experts consulted at the Conservation Foundation during September, 1952

Dr. David Bishop, Carnegie Embryological Laboratories, Baltimore (September 11)*
Dr. George Corner, Director, Carnegie Embryological Laboratories, (September 9)
Dr. Karl T. Engle, Professor of Anatomy, College of Physicians and Surgeons, Columbia University (September 18)
Dr. Jules Freund, Public Health Research Institute of the City of New York (September 17)
Dr. Michael Heidelberger, Professor of Immunology, College of Physicians and Surgeons, Columbia University (September 11)
Dr. Georgianna Seeger Jones, Assistant Professor of Gynecology, Johns Hopkins School of Medicine (September 12)
Dr. John MacLeod, Associate Professor of Anatomy, Cornell University Medical School, New York (September 17)
Mr. George Merck, President, Merck Company, Rahway, New Jersey (September 19)
Dr. Warren O. Nelson, Professor of Anatomy, State University of Iowa (September 15)
Dr. Albert Tyler, Professor of Embryology, California Institute of Technology, Pasadena, California (September 11)

* Date in parenthesis refers to day of attendance at working group session. See Appendix II.

Mr. William I. Lourie Jr. served as special assistant to the Working Group.