LONG TERM HAZARDS IN IMMUNOLOGICAL METHODS OF FERTILITY CONTROL

By

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ABSTRACT

Long term problems associated with future immunological methods of fertility control include the following: (1) reversibility, (2) unscrupulous use, (3) unphysiological intervention giving rise, among other possibilities, to carcinogenesis, (4) deleterious genetical selection operating on antigens, and (5) deleterious genetical selection operating on the immune response. The first three of these constitute a hazard to individuals, and the last two to populations. None is considered to constitute a threat so serious as to inhibit further research on the subject. We should keep under review future developments in relevant areas of immunology, including particularly cell-cell cooperation as a mechanism in autoimmunity, and immune response genes as the objects of immunoselection. It will be important also to come to terms with the social, political, and economic consequences of any cheap, widely-applicable form of birth control, such as might develop from immunological research.

The possibility is raised of wide-spread immunisation against a synthetic immunological determinant, as an aid to fertility control. Another possibility is to make women grandchildless.

This essay begins with a discussion of future immunological methods as an example of any cheap, long-lasting and efficient means of fertility control. It will then mention some of the hazards which are unique to immunologically-based methods.

Since few examples of successful control of fertility are known, even in animals, we can only guess at what may be possible in the future. The best
we can hope is that one-shot immunisation can be used to engender long-term sterility. This hope has two justifications. One is that childhood vaccination can produce life-long protection against infectious disease. The other is that the underlying mechanism — immunological memory as it is termed — is quite well understood. We can identify at least three components in immunological memory, any one of which could probably ensure life-long duration of immunity: sequestration of antigen in potentially immunogenic form (Mitchison 1969), expansion of clones of T and/or B lymphocytes (Raff 1973), and long-lived (T) lymphocytes (Buckton et al. 1967). Life-long immunity cannot always be obtained, however, and for many diseases revaccination at regular intervals is required.

Restoration of fertility

In principle one can identify several possible stages in the reversibility of sterility produced by immunisation. Stage one would be a state of sterility which would be life-long and totally irreversible. Presumably gamete storage would offer the only way round stage-one sterilization. In stage two, sterility would be life-long unless deliberately reversed. The reversal might itself be transient or permanent, and might well involve a more elaborate procedure than that originally required to induce sterility. Stage three sterility would be transient, and would require repeated re-immunisation in order to be maintained. In addition one can suppose that sterility would be either complete or partial. If it were partial, the need for reversibility would be less. The most complete, but not necessarily the most desirable, form of control would be one which is complete but reversible.

None of these options fall outside the realm of immunological possibility, as we know it from animal experiments. Deliberate reversal of a state of immunity is tantamount to the induction of immunological tolerance. Used in its widest sense this term includes methods based on mechanisms of clone elimination, active suppression, or blockade of lymphocyte receptors (Mitchison 1973; Howard & Mitchison 1974). These methods have been worked out mainly for well defined, soluble antigens such as serum proteins or microbial polysaccharides. They should, therefore, be easily transferable to an antigen such as human chorionic gonadotrophin, but less so to sperm surface antigens. However, information is starting to become available for cell surface antigens, particularly those of the red blood cell. Nearly always immunity turns out to be more difficult to stop than to start. The sort of procedures which are known so far include repeated injections of antigen over a period of months, or the injection of very large amounts of antigen. The best methods of reversal may emerge from the work which is being carried out at present on specific suppressor factors.
Methods with stage three-type reversibility would not seem to pose general problems not already encountered with other methods of fertility control, and methods with stage one-type reversibility (i. e., irreversible) might prove unacceptable. Stage two-type methods differ most radically from existing methods of fertility control, offer the greatest benefits, and pose the greatest dangers. Their greatest potential benefit is their cheapness and simplicity. This would make them particularly valuable to developing countries. Within any one country they would counteract the tendency of existing methods to reach preferentially the rich. The sociology of fertility is a tricky subject but it seems likely that the cheaper a contraceptive method is, the less it will tend to perpetuate inequality.

Their greatest danger lies in unscrupulous use. One can imagine one group of countries sterilizing another; a ruling class sterilizing a non-ruling class; widespread sterilization but restricted reversal; or a lunatic sterilizing us all. My own opinion is that these dangers are not so great that a conscientious scientist should refrain from this sort of research. But the dangers are there in any form of cheap, poorly reversible form of fertility control, and they deserve to be brought to light.

Is immunological intervention “unphysiological”?

Turning now to specifically immunological considerations we should look to start with at a sweeping objection. It runs as follows. We ought to think twice before intervening in any physiological system. Endocrine intervention can only be accepted as a method of fertility control because it is so popular, and because it has begun to stand the test of time. If all the hazards of endocrine intervention had been thought through to start with, no responsible body could have sponsored its introduction. The same considerations should prevent WHO from sponsoring immunological intervention. This objection would gain special force if the use of powerful adjuvants were included in the programme, for these might have unforeseen effects on other branches of the immune system. A consideration relevant to this objection is the involvement of the immune system in cancer surveillance (Good 1973; Mäkelä 1973). One might counter-argue that this strengthens the case for any form of non-specific potentiation of the immune response, on the ground that more immunity means more surveillance and therefore less cancer; but this is too simple a view, since one arm of the immune response might well counteract the effect of another (Mitchison 1974).

While these objections make some sense, they tend to neglect a basic difference between the immune system and other physiological systems. The endocrine system, for example, normally develops without outside intervention, and the procedures used for fertility control do therefore disturb the normal
function of the system. This is not true of the immune system: without outside intervention in the form of antigenic stimulation, normal development does not occur, and the normal function of the system is to respond to just such intervention.

It might still be argued that stimulation by environmental antigens is very different from stimulation by antigens related to self, of the type contemplated for use in fertility control. How seriously one takes this point will depend on how far one believes that the immune system is engaged in a continuous reaction against self, in a controlled manner which exercises homeostasis against autoimmunity via production of blocking factors. I find this concept far-fetched (Howard & Mitchison 1974), and therefore take the danger of autoimmunity seriously.

Cross-reactive autoimmunity

For the immunised individual, as distinct from the immunised population, the greatest hazard of immunological fertility control lies in autoimmunity. The danger is that an immune response directed at sperm antigens or antigens apparently associated only with pregnancy, will act on other tissues, engendering a form of autoimmune disease.

Autoimmunisation of this type could occur through three possible mechanisms. One of these is through shared antigenic determinants: a complex antigen used for immunisation may contain components identical with those present in other tissues. Sperm, for example, share surface antigens with neuroblastoma cells that can be detected with xenoantiserum (Artzt et al. 1973). More relevantly, alloantisera recognize the antigen Ia on both mouse sperm and mouse lymphocytes (MacDevitt, personal communication).

A second possible mechanism is steric overlap between non-identical but structurally related antigens present in different tissues. While this is the mechanism which has attracted most attention in the course of investigations on purified antigens, its importance in cross-reactions between tissues is more doubtful. There are several examples of cross-reactions, probably due to steric overlap between environmental antigens and antigens of the mammalian cell surface, among which the best known is that of the ABO blood group.

The third mechanism is spread of the response from one determinant to another on antigenic fragments via cell-cell cooperation. An example of this would be the expansion of the B cell response to haptens that is brought about by the reaction of helper T cells with carrier determinants (Mitchison 1971). In order for this effect to operate the determinants recognized by T and B cells have to be carried on the same physical structure – there has to be a bridge between determinants. It is not yet clear whether the physical structure in question has to be a single macromolecule, or whether several macromolecules
which are processed by the immunological system as a single unit can provide
the requisite bridge.

The cell-cell cooperation mechanism has a special role to play (Howard &
Mitchison 1974) if one accepts the evidence that T and B cells have a different
threshold of response. T cells appear to have a sensitivity several orders of
magnitude (approx. 3) more than B cells in the induction of tolerance by the
clonal-elimination mechanism. Consequently many self-antigens may have
B cells which are prevented from reacting to them only by the absence of
T helper cells. B cell autoimmunity can therefore develop whenever new
determinants recognised by T cells are inserted in their vicinity, e. g., as a
result of viral infection. Thus one can imagine the following succession of
events. An individual is immunised with a fragment of the β sub-unit of
human chorionic gonadotrophin (HCG) which is not present in any of the
other peptide hormones, or elsewhere in the body (Stevens 1974). Not only
B cells but also T cells react. The T cells can now serve as helper cells, and
start to present other parts of the host’s own β sub-unit to B cells. These B cells
then produce antibody which cross-reacts with luteinising hormone (LH). From
there it is only a step to the response spreading right through the pituitary
hormones, via cross-reactive sub-units. The data at present available con-
cerning the response to HCG suggest that this may be too gloomy a scenario.
Nevertheless, there does not seem to be any reason in principle why the
immune system should not operate in this way. A further complication is
added by the possibility of T-T cell cooperation operating in fundamentally
the same way, and already evidence of the need for a physical bridge in cell
mediated immunity can be cited (Pearson et al.).

So far as the WHO programme is concerned, there are two morals to draw.
One is that very careful screening for autoimmunity should form an indis-
pensible part of the evaluation of any immunisation procedure. The second is
that the WHO Expanded Programme should keep abreast of new developments
in cellular immunology, particularly those in the area of cell-cell cooperation
which are relevant to the spread of the immune response from one determinant
to another.

The case for immunisation against a universal helper determinant

The idea that cell-cell cooperation may cause spread of the immune response
can be generalised. Stevens (this Symposium) has investigated the possibility
that the immunogenic capacity of HCG can be increased by derivatisation
with PABA (p-amino-benzene-sulphonic acid). Although this particular in-
vestigation has not yielded clear-cut results, there are more successful pre-
cedents (Iverson 1970). In general terms, the hope is that the response to a
weak antigen can be enhanced by coupling it to a strong antigenic deter-
dominant, because T cells reacting to the strong determinant will help – in the
strict immunological sense involving cell-cell cooperation – the reaction against
the weak determinant. This provides one of the few logical approaches to
cancer immunotherapy, and that is quite enough to ensure that the idea will
not die untested (Mitchison 1974).

PABA may not be the best determinant to use; arsanylic acid, which has
been found to stimulate T cells preferentially (Alkan et al. 1972), might be
better. At any rate, a case can be made out for selecting one such determinant,
and then deliberately raising T cell immunity to it widely throughout the
human population. Once such immunity has been established, e.g., by skin-
painting, the correspondingly derivatised antigens should be more immunoge-
nic. This makes sense in terms of known immunological mechanisms, and
has been demonstrated experimentally in mice (Iverson 1970). The heightened
responsiveness thus engendered could be utilised not only for fertility control,
but also for cancer immunotherapy and possibly for other forms of medical
treatment. One can hardly object much to skin-painting, for this form of
treatment applied with DNCB (dinitro-chloro-benzene) has come to form part
of the standard clinical investigation of suspected T cell deficiency.

Grandchildless: a modest proposal

Every geneticist knows of the mutation in Drosophila subobscura called
grandchildless. It puts into one’s mind the possibility that some of the problems
of fertility control could best be handled by establishing such a condition in
man, thus solving the population problem by delayed action. Synchorial placentas
in cattle and some other mammalian species permit the exchange of endocrinologically active tissue, which results in the production of sterile free-
martins. This is relevant to the present discussion because the exchange is an
example of natural immunological intervention, which causes the resulting
chimaeras to become immunologically tolerant of one another’s tissue. Proce-
dures are known which induce fused placentas in mice (McLaren & Michie
1959): should they be applied in man?

Selection operating on antigens

The hazards we have so far discussed apply to individuals. There are others
which apply to populations. These are mainly those which result from the
selective pressure that would be exerted by any even moderately successful
form of immunological control of fertility. One way in which genetic selection
could operate would be on genes controlling the target antigens. Thus if con-
trol were to be exercised by immunisation against LDH-X (a putative sperm
antigen), there would be selection in favour of deletion of the enzyme if this
were compatible with sperm viability; selection would also favour antigenic variants of the enzyme, and anything which impaired expression of the enzyme antigen at the cell surface. In a general way selection against sperm antigens belongs to the category of haploid selection, and other things being equal can be expected to diminish the fitness of the diploid organism.

Sperm surface antigens have been elucidated by recent work on the alloantigens H-2 (Goldberg et al. 1970), H-Y (Bennett & Boyse 1973), and Ia (McDevitt 1974), and on the neuroblastoma antigen mentioned earlier (Artzt et al. 1973). All these antigens can be detected on the sperm surface, but the indications are that they play a less important role there than they do elsewhere in the body. This emphasizes the genetic hazards associated with immunoselection against sperm surface antigens. It must be admitted, however, that the argument is rather circular, for the antigens in question were chosen for examination precisely because of their importance elsewhere.

Another point which is worth making in this connection is that expression of some of these antigens is incomplete: some sperm evidently have more than others, perhaps because of different rates of maturation. Immunoselection can therefore be expected to influence sperm maturation – yet another complication.

In some ways the ideal form of fertility control would be one which operated on the sex ratio. Insofar as parents go on having children in order to produce males, anything which increases the relative frequency of male offspring will reduce the birth rate. From the immunological standpoint it is unfortunate that so far only a Y chromosome-associated antigen has been detected on sperm. Nevertheless X-associated antigen(s) have been identified on somatic cells in mice (Bailey 1963), and these are obviously the sort of antigen to go for in order to produce the desired effect on the sex ratio.

Selection operating on the immune response

The most severe hazard posed by immunological methods of fertility control is the selective pressure that they would impose in favour of immunological cripples. Any system which uses the immune response to limit fertility must favour the reproduction of individuals who make a diminished response. This is most obvious in the case of the gross immunodeficiencies – agammaglobulin-aemic and the like – but in a statistical sense the same effect will operate in favour of the numerous minor genes which lower responsiveness.

One can look at the pattern of genetical control of the immune response from two points of view. One is to regard immune responsiveness as a quantitative characteristic, analogous say to body size. From this point of view the best available information comes from a selection experiment performed on the immune response in mice (Biozzi et al. 1970). This has shown that the response can be shifted by selection through several standard deviations, but
that plateaus are eventually reached at a low as well as a high level. The plateaus can be attributed to loss of genetic variation. Selection alters the frequency of numerous genes. Heritability can be measured with some precision; a value of 0.36 was obtained during the early stages of selection, although this can be expected to fall as the plateaus are approached. In these respects the inheritance of responsiveness conforms to the pattern established for body size (Falconer 1953). Finally, and this is what is most sinister from the present standpoint, selection operating on one response (in this case to sheep red blood cells) markedly influences the response to other antigens; i.e., genetic correlations operate between different forms of the response.

One could enter a more detailed discussion of the response to be expected from the selection differential imposed by fertility control, using various model systems. At present the exercise does not seem worthwhile, partly because the selective system is so ill-defined, and partly because heritability is likely to alter as selection proceeds. Another reason for postponing discussion is that Dr. N. Fiengold has made a splendid analysis of the Biozzi data, which has not yet been published.

The other point of view one can adopt is to examine the mode of action of the immune response (IR) genes. Two important groups of genes have been identified, one of which controls the antibody combining site and the other more mysterious structures closely linked to the major histocompatibility loci. No doubt these functions are discussed elsewhere in this Symposium. Selection imposed by fertility control can be expected to act on these genes. This implies that one could monitor the response to selection by following changes in gene frequency at the major histocompatibility loci. A fuller understanding of the mode of action of the IR genes would tell us more about the genetical consequences of immunoselection. This again is a matter which the WHO expanded program should keep under review.

ACKNOWLEDGMENT

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REFERENCES

DISCUSSION

Cinader: I would obviously not disagree with Dr. Mitchison's emphatic call for methods which are cheap. However, we must clarify what we mean in asking for a cheap method. The danger of harmful side effects must appear in the balance sheet of expenditure. A method that is extremely cheap but has considerable risks of undesirable side effects is clearly not acceptable. The problem of social inequality—stressed by Dr. Mitchison in other contexts—arises again, in this context. A risky technique of birth control has the propensity of increasing inequality; those who require the cheap methods would incur dangers that others do not incur. To talk of "expensive and cheap", without identifying the nature of the components which must be cheap, could lead to a naive interpretation of the relevant economic factors; I am sure that this is far from Dr. Mitchison's intentions. At any rate, let us attempt to define the concept. I suggest that expensive should mean labour-rich in the delivery of care; any technique that requires an extensive health service and, therefore, puts an additional burden on the health services which are already overloaded, is obviously expensive in an undesirable sense. On the other hand, any technique which is simply expensive because a big central machinery of production is required would, obviously, become cheaper the more experience is gained and the more productivity is required of this machinery. In fact, a technologically sophisticated product will not be expensive in the long run and will become cheaper, as time goes on and as demand increases. In short, we should seek safe techniques free of side effects and not requiring
advanced medical intervention in health care delivery. We should not demand that these techniques shall be developed “on the cheap”.

Southam: You classified immunological methods as being of either long duration or short duration. I think there is an important additional classification, that would be the use of passive immunity at the time of a missed period. This would be used maybe twice or three times a year and I think that would be an ideal method.

Miller: I think there is another classification that should be considered, and that is systemic immunization versus local immunization in the mucosa.

Fudenberg: While we are engaging in what might perhaps be a new sub-branch of immunology, “immunophilosophy”, I would like to try to be a bit more precise. Dr. Mitchison said the “cost of developing and propagating”. I think one must separate those two, because some things that are extremely costly to develop are extremely cheap to propagate. Further, if something works scientifically it soon becomes cheap because so many people want to use it. The best example I can give is perhaps some of the pocket calculators which have dropped in the past year to one sixth their initial price. One other point is – Dr. Mitchison’s statements, at least to me, imply that one method of fertility control will suffice. I think each country will perhaps prefer several methods, surely citizens of different countries will differ in the methods they prefer. Further, at least at this stage, we do not know which method will have the least number of undesirable side effects or the greatest severity of side effects and also which would be the most effective, hence, I believe that trying to restrict ourselves to one method, as perhaps you imply, would be a mistake.

Pernis: Dr. Mitchison said that the most expensive method in principle should accentuate and perpetuate social inequality. At first sight it might seem that the reverse should happen, because the most expensive methods should have the tendency to reduce the progeny of the more wealthy families, eventually they would be wiped out completely, and this is not in the direction of accentuating inequality.

Nossal: The chair, recognizing the fascination of immunophilosophy, will now nevertheless entertain a few questions only on the subject of duration. What do the immunologists feel at the prospects for the relative three phases that Dr. Mitchison discussed?

Waldman: I don’t know that long duration, or permanence, is going to really be a problem one way or the other. The only cases where permanent immunity exists are following viral infections in which there is very good evidence that there is persistence of antigen. If one takes all the other examples of immunization, the duration is not extremely long, thinking in terms of 20 or 30 years, and, for example, with tetanus toxoid one has to boost every ten years or so. Unless one can develop an immunization in which there is some sort of latency of the antigen, persistence of the antigen, I do not think permanence is ever going to be achieved, so the question of whether it is desirable or not may be irrelevant.

Fudenberg: Shatton (1955) published an example of a woman who still had anti-Rh antibodies 20 years after she received a blood transfusion with Rh positive blood. She received no blood transfusion since then. The interpretation has been immunity to the Rh antigen may last for 20 years. However, in terms of what we heard to-day, perhaps Rh antigens are present on sperm, so that she was continuously reimmunized.
Voisin: Dr. Mitchison spoke of irreversible versus long-acting methods and of expensive versus cheap methods for an immunological control of birth rate. Do we actually have a choice between several efficient methods? I would like to have only one or two of them, and I am sure that we could not afford to require them, in addition, to be cheap (if they are efficient, they will eventually become cheap).

Mitchison: I was not saying what we can and cannot do. I merely pointed out that there is a logical relationship between durability and cheapness and there is a logical relationship between cheapness and equality.

David: This has to do with the question of duration of immunity. I would think this is still an open question. Using sperm antigen, for instance, long-lasting immunity might be present due to constant natural boosting of the immunity, and 20 years during the child-bearing age might be considered as “permanent”.

Nossal: Turning our attention to problems related to autoimmunity and cell-cell cooperation both Dr. Stevens and Dr. Talwar insisted upon the use of modified antigens, particularly Dr. Stevens having made a strong point about the relationship between the degree of immunogenicity and the degree of conjugation with hapten. He did not elicit delayed hypersensitivity, i.e., did not get the T cell system going, but only the B cell system. Isn’t this evidence for T cell tolerance for the native hormones present in the circulation? In other words, you are sparring with a shadow.

Fudenberg: Your mention of universal immunization brings up a point. If we are discussing trials, I am sure that no one here would consent to a universal trial, I would urge separate trials of any given method to be carried out in several different countries at once based on a former experience. Some years ago, as you know, about 98% of the population of Denmark was immunized with a batch of polio vaccine which was grown in monkey kidney contaminated by polyoma virus. If 98% of the population of Denmark comes down with cancer twenty years from now, we will be accused of genocide, hence, I believe that any pilot studies should be carried out in several different countries simultaneously.

Nossal: The caveat that you put about endocrine regulation being a sort of an internal clock was intriguing. Would you therefore exempt from the broad blessing that you gave to the immunological approach those immunological approaches that seek to vanquish hormones?

Mitchison: No.

Nossal: I don’t see, in principle, how the objection to oral contraceptives are any different from the objections to anti-HCG.

Mitchison: Yes, it is a good point.

Ryan: I would not accept Dr. Mitchison’s facile explanation, or comparison between immunological mechanisms and endocrine ones. After all, the endocrine system developed on an evolutionary basis in a way that requires individuals to interact with their environment and other individuals in order to reproduce. It is not a self-contained internal system.

Talwar: I think the immunization approaches against subunits of HCG can still be sustained, because this hormone is not a normal part of the self-regulatory feedback system. It differs from the pituitary hormones and the target organs in that respect.
Such immunizations should not intervene in the endocrine internal regulation as long as there is no crossreaction with LH and other hormones.

May I raise one more point, and this is on the use of haptens and their potential for generation of possible autoimmunity. I would like to be clarified about the implications of several reports showing that many myeloma proteins have antibodies which are reacting with a variety of haptenic groups. I think this evidence may be critically examined to see whether we are not falling into yet another type of complication. I would also like to add that in our hands loading the DNP in graded doses on beta subunit of HCG in concentrations which are immunogenic but not drastically altering the conformation of the molecule, the type of antibodies formed did not have the same degree of high affinity and desirability in their biological properties as the antibodies raised to the conjugates of beta HCG with proteinic carriers.

**Askonas:** One more point before we leave the problem of immunological endocrine intervention. Are we sure that long term immunization does not damage the endocrine organ which produces the hormones? I think this should be checked carefully in long term follow-up of experiments.

**Talwar:** HCG is produced by the trophoblasts. They are not normally part of the female physiology, unless conception takes place.

**Askonas:** Yes, but destruction of the trophoblast could lead to autoimmunity and antibody-antigen complications, which could be rather dangerous.

**Talwar:** The endocrine system is not a part of the normal homeostatic circuitry. Neutralization of the HCG support at the early stages of conception would cut off the corpus luteum function, resulting in the induction of menstruation.

**Amos:** In designing some form of intervention, perhaps it would be desirable to concentrate on single components of the immune system because then regulation would be so much easier. I would have thought that one would almost of necessity have to pursue four separate lines including the one which you have been concentrating on, of immunity to the endocrine system. Dr. Southam earlier commented on the need of women for passive immunity once or twice a year to prevent or to terminate an early pregnancy. One would also want an active type of seroimmunization directed at the pre-implantation stage. Then probably the most effective, but of limited duration, would be the development of a form of cellular immunity effective at the time of implantation. Different components of immunological prophylaxis would be applicable to different degrees of development of a civilization and religious ethic. For example, destruction of a fertilized ovum might not be acceptable to Roman Catholics because it terminates a pregnancy. Some of the procedures would not be applicable to poorly developed countries.

**Southam:** In the United States almost as many Catholics as Protestants seek abortion.

**Diczfalusy:** I would like to address myself to the question raised by Dr. Askonas, which is certainly very important. If we are looking into the endocrine system in general, there are relatively few data but there are data on animals immunized with steroid complexes, with bovine serum albumin complexes, and there is no doubt that in rabbits, for instance, in whom antibodies are produced to testosterone, there is an enormous hypertrophy of the Leydig cell apparatus and there is a greatly increased secretion of testosterone. Whether this can lead, in the long run, to very serious consequences, remains to be seen.
Cinader: The suggestion, that grandchildless birth control should be contemplated, deserves careful scrutiny. Dr. Mitchison has addressed himself to the general problem of inequality. At the same time, he has contemplated a measure which would have profound effects on the structure of society and on social evolution. In fact, an inequality would be created which would be more fundamental than any other consequences of economic and social inequality. Clearly, he would not have an entirely grandchildless population; a cast of people would be created which would be barred from having descendants. There are profound ethical objections, but these are too obvious to need discussion. What may be less obvious are the effects on the evolution of social structure. Animals which have had the longest period to evolve a collective existence have done so by exploiting polymorphism and by reserving sex to a very small number of individuals; the majority of the population does not procreate. This works superbly well in removing obstacles to cooperativeness in those whose functions are confined to social service. This could be the destiny of man! Dr. Mitchison’s proposal might accelerate the process. Other mechanisms intensifying polymorphism, such as the preservation of genetic deficiencies which would create individuals entirely dependent on health care, might be additional propellants. Before grandchildless birth control is seriously contemplated, we should decide whether we intend to strive for the ant model or whether we would like to evolve a vertebrate variety of social cooperation which is not based on sexual specialisation. Perhaps there is a choice to be made between social evolution driven by the individuals’ absolute dependence on society and social evolution driven by the moral indignation of the maverick.

The second point to which I would like to address myself, also concerning polymorphism, is the need for an instrumentarium of different methods of birth control. This need was justified, in terms of religious and social heterogeneity in the resistance to birth control. One might doubt whether such motivations would really deter people from using an effective and harmless method of birth control, once the need for population stabilization has been accepted. Nevertheless, sets of alternative methods must be developed because of the molecular polymorphism of human populations. As a consequence of this polymorphism, almost any technique might be ineffective for some individuals, and will have undesirable side effects in others. Thus, independent approaches are required.

Goldberg: Certainly the immunoselection point is significant. I would suggest, however, that it would be no more significant for immunological fertility control than for any other type of fertility control. For example, we might select in favour of the population of women susceptible to nausea because they cannot take the Pill.

Nossal: You stressed the importance of antigens present on the sperm and the fact that the sperm might not work well if they were not present. Surely, a crucial part of your argument must relate to the degree of heterogeneity of antigen expression on sperm. If it is true that the sperm in order to work has got to have HL-A, T and IA, then your argument in a sense breaks down, because there is no selectivity. Those sperm that have those antigens are destroyed by the vaccination procedure. Those sperm that don’t have them don’t work, so could you clarify in detail why you think this is a dilemma here.

Mitchison: This is a significant point. There is evidence of heterogeneity in the case of H-Y which is believed to be related to maturation. Immunoselection operating on antigens could select for slow maturing sperm.
Ryan: I would like to say a word about the freemartins. I am not aware that it is an immunological form of sterility. Secondly, one of the pair is sterile, the female, and in the primates where there are blood group chimaeras as a result of an exchange between non-identical twins, freemartins do not occur.

Behrman: From a practical standpoint, assuming one has a form of immunization, the target being either sperm, placenta or some other reproductive site; and assuming that it is effective to an acceptable point, what happens at the point of reversibility, i.e., where there may be “breakthrough” or antigenic “escape”? Is there an immunological way of turning off your vaccine?

Mitchison: In all systems that I know of it is a lot harder to turn a response off than to turn if on. Anybody can turn a response on, but it is a very skilful job to turn it off.

Franklin: Perhaps one may not have to rely on immunologists to turn it off. In a system such as we have here, we are relying on a very small active peptide. Maybe we can rely on a peptide chemist to synthesize an analogue that has biological activity and is no longer reactive with the immune system.

Reference: