THE TENTH OLIVER BIRD LECTURE

FERTILITY CONTROL:
ACHIEVEMENTS AND PROSPECTS*

G. I. M. SWYER

University College Hospital Medical School, London

INTRODUCTION

I am very sensible of the honour accorded to me today by the Oliver Bird Trustees in inviting me to give this, the 10th Annual Oliver Bird Lecture. I am particularly glad that you, Professor Parkes, should be my chairman on this occasion, just 20 years after you accorded me the privilege of becoming a member of your staff at the National Institute for Medical Research. I was then very much an amateur in the field of reproductive physiology and, looking back, I have the impression that most of my colleagues were also amateurs, in the best possible sense. The days of the rat-race, of fierce competition and of, one might almost say, brittle professionalism, had not yet begun. Our interests were then more closely concerned with the promotion of fertility than with its control in the negative sense, and we had not yet become alarmed about the population explosion. Even so, our Chairman, more far-seeing than most, had, in a lecture on population given at the National Institute in 1946 (Parkes, 1946) sounded some notes of caution. I cannot deny myself the pleasure of quoting Professor Parkes' opening remarks in that lecture: "The study of population, or demography", he said, "must concern itself with politics, religion, sociology, psychology, biology and statistics. This is an explosive mixture . . .". How right he was to use that word 'explosive'.

Twenty years ago there were few who were aware of the rate of expansion of the world's population, or who gave much serious thought to it. In making his famous speech at Fulton, Missouri, even Winston Churchill, in 1946, so lacked his customary foresight as to see fit to quote words used 50 years earlier by Bourke Cockran, his Irish-American friend of those days: "There is enough for all. The earth is a generous mother; she will provide in plentiful abundance food for all her children if they will but cultivate her soil in justice and in peace". And Churchill cannot have forgotten his experience of the teeming cities of India. True enough, Robert Malthus, born just 200 years ago, had become very much concerned about these matters, but he was far in advance of his time. In 1949, when the United Nations convened a scientific conference on world resources, Sir Julian Huxley, then Director General of UNESCO, suggested that a survey of resources should be accompanied by a similar survey of the population which consumed those resources. He has written (Huxley, 1957): "I was told that there were technical, political and religious difficulties. Eventually

* Delivered at the School of Hygiene and Tropical Medicine, London, 2nd February 1967.

these difficulties were smoothed over; censuses were taken; and a conference on population was duly held in 1954. During the 5 years it took to arrange for a look at the problem, the world's population had increased by more than 130 million." In the 20 years since Professor Parkes gave his lecture on Population, the world's inhabitants have increased by almost a thousand million. The previously slow growth, over many millennia, of the world's population beguiled most of its inhabitants so that realization of the impact on population increase of scientific death control, when at last it was introduced, has been slow to dawn. The rate of increase obtaining now is of such a magnitude that the mind boggles at the consequences. At 2 to 3% per annum for more than half the world's 3000 million and more inhabitants, "Mankind", to quote Huxley (1957) again, "will drown in its own flood". Professor Ansley Coale of Princeton has predicted that: "In about 6500 years (approximately the period of recorded history), if current growth continues, the descendants of the present world population would form a solid sphere of live bodies expanding with a radial velocity that, neglecting relativity, would equal the velocity of light". Others have offered equally dramatic representations of the effects and consequences of what present world population trends presage for the future, but there is no need to stress the point further. The fairly obvious conclusion, that it has become necessary to match scientific death control with scientific birth control, though, incomprehensibly, still rejected by some, is being accepted by increasing numbers of responsible people. Scientists of the highest calibre and fund-granting organizations of standing to support them, have been turning their attention in increasing degree to this problem and to the methods that might be employed for its solution.

To his great credit, the late Captain Oliver Bird realized the calamitous possibilities earlier than most and, 10 years ago, by the munificent gift of £30,000, he founded the Oliver Bird Trust, to further the development of improved methods of birth control.

Now, as the 10th Oliver Bird Lecturer, it has seemed to me not inappropriate to take stock of what has been achieved in the expanding realm of fertility control and to attempt to lift a corner of the veil that hides the future developments in this field. The nine Oliver Bird Lecturers who have preceded me are of such eminence and standing, and are all responsible for such profound contributions to this field, that I am bound to feel very humble in attempting to follow them and to be all too aware of my shortcomings for the task.

The wisdom of the Oliver Bird Trustees is apparent from the choice of former lecturers and from the breadth of the subjects of their lectures. It is interesting to note that Dr T. Mann, the first Oliver Bird Lecturer, chose as his subject, 'The biochemical basis of spermicidal activity' (Mann, 1957). Scientific though his approach undoubtedly was, the use of spermicides as a means of birth control would now scarcely be considered as coming within the realm of 'scientific birth control'—a measure, one may say, of the extent to which thinking on this subject has moved on.

In recent years, increasing interest in the subject of fertility control has led to the convening of a number of symposia and the publication of several works recording their deliberations. Though this has, in some ways, lightened my task

in surveying the achievements, it has also faced me with a veritable *embarras des richesses*. I must of necessity be selective and that means liable to errors of omission. Taking the narrow, even if, ultimately, the most important view—the control of human fertility—the achievements are few in number. The oestrogen/progestagen oral contraceptive and its recent developments, and the intra-uterine contraceptive device are in use and, if their use were to be on a sufficiently wide scale, they could, at least in theory, certainly arrest excessive population expansion. Indeed, there is evidence that, in limited areas, they are already doing so. Taking a broader view, the scientific study of agents affecting fertility has made advances on a very wide front and it is this I would now like to survey briefly.

ACHIEVEMENTS

ANTIFERTILITY AGENTS OF PLANT ORIGIN

The use of plant preparations for the control of fertility by primitive peoples is the subject of numerous reports, some published, others merely verbal, but information which would stand up to critical evaluation is extremely scanty except in the case of the plant oestrogens. More than fifty species have been reported as having oestrogenic activity (Bradbury & White, 1954). In most instances the chemical nature of the oestrogens has not been defined but some have been characterized, including, particularly, isoflavones and related compounds (Price, 1965). A number of other substances of known chemical composition, many of them alkaloids such as pilocarpine, physostigmine, morphine, colchicine and the peltatins, have demonstrable anti-fertility effects in experimental animals. Many more, of unidentified composition, may or may not have such effects. Of these, perhaps the most extensively studied is the extract of the roots of *Lithospermum ruderale*, said to have been used by the Indians of Nevada for controlling fertility. Though the extract appears to possess anti-gonadotrophic properties, all attempts at separating the active principle, even in crude form, have proved unavailing.

It may be doubted whether exhaustive searches through anthropological literature and the testing of hundreds of species of plants in the hope of finding effective agents for fertility control is justified. The reason for doing this, of course, is that such studies might offer a lead from which, by the preparation of chemical analogues, highly effective agents might be derived. So far these hopes have not been realized.

VITAMINS

The discovery of vitamin E by Mathill & Conklin (1920), more than 45 years ago, during the course of experiments on reproduction of rats, was the first indication of specific nutritional factors affecting fertility. Vitamin E, as well as vitamin A, has many roles in physiology apart from that involved in reproduction and these two vitamins, though commonly regarded as particularly concerned with reproductive processes, are only two of many other nutritional factors so concerned (for a review see Moore, 1965 and Thompson, Howell & Pitt, 1965). To the possible consequence of this for the future I will return later.

AGENTS AFFECTING MALE FERTILITY

Last year's Oliver Bird Lecturer, Dr Carl Heller, concerned himself with the male and showed that, contrary to what might generally be supposed, a lot more is known, and with a lot more precision, about agents affecting fertility in the male than in the female. I cannot, for obvious reasons, attempt so detailed a treatment as Dr Heller's but nevertheless I must attempt to do no less than justice to this not unimportant sex within the context of my subject.

In the first place, I may remind you that the inhibition of spermatogenesis is readily brought about by substances, mostly steroids, which attack the pituitary-testis axis. Of these substances the most potent are oestrogens, the anti-androgenic action of which precludes their potential use as male contraceptive agents. The subject has recently been fully reviewed by Pincus (1965) in his book *Control of Fertility*. However, Harold Jackson (1965) contends, and probably rightly, that control by interference with overall hormonal mechanisms has no real prospect of success and goes on: "We are therefore faced with developing chemical agents which will impair the process of spermatogenesis more or less directly. The basic pharmacological theme is thus chemical interference with one of the many and varied proliferating cell systems in the body, with the specific requirements for a drug of acceptability, selectivity, rapidity and predictability of action. It should be borne in mind that work of this nature has only seriously been in progress for the last ten years or so, and on a very limited scale." Most of it, incidentally, by Jackson and his colleagues.

Drugs may affect spermatogenic cells in two general ways: they may either inhibit cell development or lead to cell destruction at some stage of spermatogenesis; or they may interfere with cell function so that, though spermatogenesis is not inhibited, the ability of the spermatozoa to fertilize and maintain development of the zygote is lost. The complex nature and long duration of mammalian spermatogenesis makes the techniques of investigation long and tedious, while requiring large numbers of experimental animals. This imposes obvious limits on the number of compounds which can be investigated.

Some of the compounds most extensively studied are esters of methanesulphonic acid. In the series of diesters methylenedimethane-sulphonate has a rapid action exerted on spermatozoa in the terminal part of the epididymis and perhaps in the vas deferens, a single dose of 15 mg/kg intraperitoneally in the rat causing sterility in the first week only. Smaller, daily doses (2 mg/kg) produce azoospermia by inhibition of the stem cells so that, on discontinuation of treatment, sterility persists for a further 7 weeks after which, a new series of spermatogonial divisions having led to the development of mature spermatozoa, fertility is gradually restored. A still smaller daily dose administered orally (0.5 mg/kg) produces marked sub-fertility which is replaced by normal fertility within a week of stopping treatment showing that, at low dosage, only the effect on the epididymal spermatozoa is involved. This compound, therefore, exhibits the two possible kinds of effect on spermatogenic cells, referred to previously (Jackson, 1965). The dimethylene compound appears to have a different effect, exerted on the spermatids, not the spermatogonia. The mono-esters of methanesulphonic acid have yet other effects on male fertility, the cells most susceptible

being spermatozoa and spermatids 2 to 3 weeks before maturity. The activity of compounds of this series diminishes rapidly as the carbon chain of the alkyl group lengthens, methyl methanesulphonate being more than eight times as active as the n-propyl ester. Comparatively small changes in chemical structure may result in distinct differences in pharmacological effect, as illustrated by the conversion of the post-meiotic action of the n-propyl compound to a pre-meiotic action (on the spermatogonia and spermatocytes) of the branched-chain *iso*-propyl compound. I have referred to these studies of Jackson's in some detail because they show the potentialities for chemical manipulation in the development of pharmacological agents with highly specific properties, which, of course, is what is required for chemical fertility control.

A number of other groups of compounds have been investigated, including nitrofurans, thiophenes, bis (dichloroacetyl) diamines and dinitropyrroles (Nelson & Patanelli, 1965). The first three groups of compounds block spermatogenesis at the primary spermatocyte stage. Although the nitrofurans and thiophenes were found to be too toxic for human study the diamines were sufficiently well tolerated to permit this and thus show that the effects in man are similar to those in laboratory animals (Heller, Flageolle & Matson, 1963). The dinitropyrroles also act on the primary spermatocyte stage and one of these, 1-(*N,N*-diethylcarbamoylmethyl)-2,4-dinitropyrrole (ORF-1616), the most active agent tested (Patanelli & Nelson, 1964), was found to be capable of maintaining sterility in the male rat indefinitely, with complete recovery on withdrawal of treatment, on a single oral dose administered at 4-weekly intervals. Compounds of the diamine series and particularly WIN 18446 have been studied on male prisoners in the United States (MacLeod, 1965; Nelson & Patanelli, 1965) and have been shown to be effective agents for the suppression of spermatogenesis. However, when given to non-prison males they were found to have an 'Antabuse-like' effect when alcohol was taken, thus seriously limiting their acceptability for possible contraceptive use, except perhaps by the abstemious.

Although animal studies of the kind to which I have referred demonstrate clearly the feasibility of drug-induced male sterility, the problems involved are numerous and complex, including such possibilities as serious effects on other systems, e.g. bone marrow, cumulative action, mutagenic effects and carcinogenicity. Undoubtedly the amount of work still to be done before this approach would have widespread human applicability is enormous.

OESTROGEN/PROGESTAGEN ORAL CONTRACEPTIVES

Though some question of priority may exist concerning who first thought of inhibiting ovulation in the human female for therapeutic purposes and of using oestrogens to achieve it, there can be no doubt that to Pincus and his colleagues must go the credit for demonstrating the effectiveness of oral oestrogen/progestagen combinations for fertility control. The first clinical studies were reported in 1954 (Pincus, 1955) and subsequent investigations by numerous observers in many parts of the world have established beyond doubt that the oral administration of a tablet containing a suitable dose of an oestrogen

(ethinyl oestradiol or its 3-methyl ether, mestrenol) together with one of a number of progestagens, from the 5th day of the menstrual cycle for 20 or 21 days can prevent pregnancy with a virtual 100% certainty.

It is fair to say that the work of the Pincus group, the subject of the second Oliver Bird Lecture by Dr Gregory Pincus himself (Pincus, 1959), ushered in the scientific era of human birth control. Though the principles involved may not have been so new, their application most certainly was. What was so remarkable about 'the Pill' was that here, at the first attempt, an almost 100% effective method had been achieved, something surely unparalleled in pharmacological history. A vast literature has accumulated on the subject over the past 11 or 12 years, much of it having conveniently been reviewed in recent books (Pincus, 1965; Mears, 1965; Drill, 1966). Of course, the pill is not the last word and some of its inconveniences were brought out in Dr Margaret Jackson's Oliver Bird Lecture (Jackson, 1962).

The precise mechanism of action is still not known with certainty though inhibition of ovulation is undoubtedly the primary pathway involved, brought about by hindering the release of gonadotrophins by the anterior pituitary gland. This, most probably, is mediated by action on the hypothalamus, inhibiting production of gonadotrophin-releasing factors so that, in turn, pituitary gonadotrophin release is prevented. Most observers agree that luteinizing hormone secretion is thus inhibited, but whether secretion of follicle-stimulating hormone is also inhibited is open to some doubt. Additional factors which may contribute to prevention of conception are the action of the progestagen on the cervical mucus, rendering it less receptive to sperm penetration; a possible effect of the steroids on tubal transport; and the development of a state of 'secretory exhaustion' in the endometrium which would discourage implantation should ovulation and fertilization have occurred.

An alternative method of administration, the sequential regimen, has been under investigation for the last 4 or 5 years. In this, oestrogen is administered throughout the 20- or 21-day course, progestagen being added during the last 5 to 10 days. The advocates of this regimen assume that oestrogen alone is sufficient for ovulation inhibition, progestagen being needed merely to ensure a satisfactory withdrawal bleeding. Oestrogens being cheap and progestagens relatively more expensive, the cost of the materials is reduced. Insofar as the pattern of hormone administration more nearly approximates that of hormone production in the untreated menstrual cycle the regimen is claimed to be more 'physiological'. Although some investigators hold the sequential regimen to be no less effective in fertility control than the combined regimen, others believe there to be a higher failure rate, especially in later cycles of treatment. If ovulation inhibition by oestrogen alone is less dependable than by an oestrogen/progestagen combination, a higher failure rate with the sequential regimen would not be surprising, especially since the additional safeguards of progestational action on the cervical mucus and of a hypoplastic endometrium are not present.

The superior effectiveness of oestrogen/progestagen oral contraception over all other available methods is not a matter for dispute but discussion still centres on the safety of the method, particularly over the long term. This has been

reported on by a Scientific Study Group of the World Health Organization (WHO, 1966), and I have myself discussed it elsewhere (Swyer, 1966). The general conclusion reached was that the vast amount of clinical information and laboratory data that has accumulated since their introduction 10 or 11 years ago, together with what was known from the clinical use in gynaecology, extending back to more than 25 years, leaves no doubt that the safety of this class of compounds compares favourably with that of most drugs in widespread use. Although the laboratory studies have shown that oral contraceptives produce changes in many body systems (as might be expected), it is doubtful if any of these have pathological significance. Serious adverse reactions, such as thrombo-embolic disease, have been reported in women using oral contraceptives, but the available statistical evidence does not establish a cause-and-effect relationship, and neither does experimental evidence. In the United States alone, where the extent of oral contraceptive use has been greatest (an estimated 5,000,000 users in 1965), there can be little doubt that the risk of death in childbirth following unsuccessful use of other methods of birth control is several times greater than the risk of dying as a result of using oral contraceptives.

Two developments under investigation at present are long-acting injectable preparations and low-dosage progestagen-alone therapy. The former makes use of long-acting oestrogen and progestagen formulations, combined in a single injection, the intention being that this be given once a month or still less frequently. Siegel (1963) found a monthly injection of hydroxyprogesterone caproate, 500 mg, with or without oestradiol valerianate, to be an effective contraceptive regimen and a number of other workers have since used different compounds for the same purpose. Of these, the most widely studied preparation has been Deladroxate, a combination of dihydroxy-progesterone acetophenide and oestradiol oenanthate (see Reifstein, Pratt, Hartzell & Shafer, 1965; Felton, Hoelscher & Swartz, 1965). Though apparently highly effective in preventing conception, the major drawback of the formulations used so far is relatively poor cycle control and a relatively high frequency of minor side effects. Whether more important long-term adverse reactions might be encountered remains to be seen. Obviously the concept, effective as it has already been shown to be, offers scope for further development.

The possibility of preventing conception with low doses of progestagen alone stems from the observations of Rudel, Martinez-Manautou & Maqueo-Topete (1965) on women given chlormadinone 0.5 mg daily from the 5th day of the cycle for 20 days. These women failed to conceive although ovulation had apparently not been inhibited. In a larger series of over 400 women, treated for a total of some 1600 cycles, some with continuous, some with cyclic chlormadinone 0.5 mg daily, ovulation was believed to have occurred in about 60% of cycles (Martinez-Manautou, Cortez, Giner, Aznar, Casasola & Rudel, 1966). In spite of this, only four pregnancies (two due to patient failure) occurred; a pregnancy rate of 2.93/100 woman years. Break-through bleeding and spotting were the principal side-effects. The simplicity of continuous treatment, without inhibition of ovulation, obviously has much to commend it and is, therefore, attracting a good deal of attention. The mechanism of action is still uncertain,

but an effect on the cervical mucus, rendering it less receptive to spermatozoa, is one of the possible factors involved, though probably not the only one.

NON-STEROIDAL GONADOTROPHIN INHIBITORS

Substances, other than steroids, with the property of inhibiting pituitary gonadotrophic function, have been investigated in recent years. They are of two main types. The first includes compounds with chemical structures resembling, even if somewhat remotely, steroidal oestrogens and having oestrogenic, anti-oestrogenic or both activities. Compounds of the second type are unrelated in molecular structure to steroids and have no direct action on the reproductive organs.

Some of the important early studies which demonstrated gonadotrophin inhibitory and stimulatory effects were reviewed by Walpole (1965) at a Biological Council symposium in 1964. He also referred to some of the more recently synthesized compounds with relatively marked anti-oestrogenic activity. These triphenyl-ethylene, -ethane and -ethanol compounds include etham-oxytriphetol (MER 25), clomiphene (MER 41), U-11,555A and U-11,100A. All four compounds have anti-fertility effects in the female in several species, the mechanism involved not being known precisely and possibly being different for the different substances. The first two compounds, and especially the second—clomiphene—have attracted interest because of their ability, in certain circumstances, to induce ovulation in women and so to promote rather than inhibit fertility.

Of the compounds of the second type—those without direct action on the reproductive organs—certain derivatives of dithiocarbamoylhydrazine have been most widely studied (Walpole, 1965). The first of these (I.C.I. 22,365) was shown to have an inhibiting effect, either directly or indirectly, on pituitary gonadotrophic function and, in the human female, to decrease the excretion of gonadotrophin after the menopause but at the same time to depress thyroid function. Some 200 compounds, chemically related to I.C.I. 22,365, were synthesized by Richardson (see Walpole, 1965) and tested for apparent gonadotrophin inhibitory effect. One of these, I.C.I. 33,828, proved to be the most potent and to have endocrine effects identical with those of I.C.I. 22,365 but to be several times more potent though without any greater toxicity (Paget, Walpole & Richardson, 1961). Anti-fertility effects were demonstrated in male rats; they began to appear even before any changes in testicular histology could be seen and declined after cessation of treatment. The effects on gonadal development in female rats were consistent with gonadotrophin inhibition. Clinical studies showed the compound to act like, but to be considerably more effective than, I.C.I. 22,365. Ovulation could be inhibited in women during the reproductive years; at higher dosage, menstruation also was suppressed, but at lower dosage (50 mg/day) ovulation could be inhibited without suppression of menstruation, at least in some women. Toxic effects—mainly anorexia, nausea, lethargy and somnolence—were experienced by some subjects at all dosage levels, even down to 50 mg/day. In its action on the thyroid gland both blockage of thyroxin synthesis and inhibition of thyrotrophin secretion have

been demonstrated. Clearly, the well-tolerated agent with a selective effect on gonadotrophin release and without other actions has not yet been found but possibilities are obviously there.

INTRA-UTERINE CONTRACEPTIVE DEVICES

Dr Alan Guttmacher's Oliver Bird Lecture in 1964 on this subject (Guttmacher, 1964) dealt with the re-introduction, thanks to technological advances in materials, of an older, largely discarded method, the potential importance of which seems profound but has still fully to be assessed. It would be needlessly repetitive for me to attempt to cover this subject as fully as it otherwise deserves and I shall content myself with just a few observations.

The advantages of the intra-uterine device are that it is cheap to produce and, after insertion, continues to act, apparently indefinitely. Its disadvantages are that it is unsuitable for use in a substantial proportion of women—most nulliparae, those who have had pelvic inflammatory disease, those who extrude it and those from whom it has to be removed because of pain or bleeding; and it does not always prevent pregnancy, the overall failure rate, in fact, being about 5/100 woman-years of use. Furthermore, in considering large scale use, as in a country like India, the cost of the device has to be reckoned as only a small fraction of the total cost of an insertion programme. Most of this cost would be made up of salaries for the medical and para-medical personnel required and that of their equipment. To have a real impact on India's 500 million and rapidly growing population, at least 3000 trained, full-time doctors, with adequate para-medical personnel, would have to work for a year to fit the 30 to 40 million women involved, while others would be needed for after-care and follow-up. What is more, during this year of strenuous endeavour there might be 10 to 15 million unwanted pregnancies among those waiting their turn to be fitted. A campaign to distribute oral contraceptives of some kind on such a scale would certainly cost far less and would have an immediate impact. It would also permit the more leisurely development of a programme of intra-uterine device insertion and thereby increase the chance of its success.

MISCELLANEOUS MODULI OF SCIENTIFIC INTEREST, BUT NOT YET OF PRACTICAL APPLICATION

It is among these that future developments for human fertility control may be found, though probably few will ever reach the stage of clinical trial. Time permits only brief reference.

Central neural blockade of ovulation. There are many drugs, such as atropine, morphine, the barbiturates, chlorpromazine, dibenamine and SKF-501, which are effective in experimental animals for inducing central neural blockade of ovulation. Nevertheless, Everett (1965) concludes that: "there is no prospect that any of the drugs mentioned here could ever serve in the practical regulation of reproduction in man or his domestic animals". However, the prospect of pharmacological control by more specific agents remains a possibility for the future.

Embryotropic agents. The control of fertility through interference with embryological development by agents administered to the mother may be thought to have only limited appeal for human use. Nevertheless it deserves, and has received, serious scientific study, some aspects of which were recently reviewed by Lutwak-Mann & Hay (1965).

Inhibition of implantation. Prevention of implantation of the fertilized egg, as a means of controlling fertility, offers certain attractive prospects, at least for those who consider conception to date from the time of implantation, not of fertilization. The fact that an agent preventing implantation could be used after coitus instead of in anticipation of it is obviously advantageous. A good deal of study has been directed towards inhibition of implantation in experimental rodents (Shelesnyak, 1965; Mayer, 1965) but the relevance of this to the human has yet to be demonstrated. To date there do not appear to have been any effective clinical studies.

Pheromones. These are agents which, secreted externally by one individual, affect the development, behaviour or reproduction of other individuals. The biological role of pheromones has been demonstrated most extensively in insects but the possibility of their playing a part in mammalian reproduction has not received much attention. The most striking revelation of pheromone action in mammals is the 'Bruce-Parkes' effect. In this, pregnancy is blocked if a recently mated female mouse is exposed to a strange male—that is, not the stud male—especially if the strange male is of a different strain. This effect is brought about by an agent secreted by the strange male, and present in his urine, affecting the female through the sense of smell and suppressing the release of luteotrophic hormone by the female's pituitary gland (see Bruce & Parkes, 1965). The possibilities for controlling fertility by substances of this class are as yet unexplored.

Immunological control of fertility. This has been attracting increasing attention in recent years and was the subject of Dr Albert Tyler's Oliver Bird Lecture in 1960 (Tyler, 1960) and so does not require extensive mention at this time. As far back as 1932, Baskin tried it unsuccessfully in the human and even took out a U.S. patent; but all the work before 1950 was controversial and of doubtful significance. The introduction of Freund's adjuvant in 1953 permitted greatly enhanced production of antibodies, but for human use a much better tolerated adjuvant will be necessary and many questions will have to be answered. A method of directly demonstrating free circulating antibodies, active at body temperature, will be needed and the specific antigen against which these antibodies are directed will have to be recognized. The path of transfer through the reproductive tract and the properties of the antibody will have to be defined.

As Behrman (1965) asks: Are the antibodies tissue-fixing? Do they deposit in the uterus, leading to an anaphylactic reaction with uterine contraction preventing sperm migration or nidation of the fertilized ovum? Would immunization with a placental antigen inhibit placentation? Could antigens from seminal plasma be used to induce a hostile environment to spermatozoa, so preventing fertilization? Can phagocytic action of the uterus and vagina on supernumerary spermatozoa stimulate antibody production, and is this enhanced

by repeated coitus? If so, why does it apparently induce infertility in only a small proportion of women? Is there a future for anti-ova preparations?

Highly specific red blood cell agglutinins have been found in proteins from various bean plants, as a result of which the so-called lectins have come into general use for typing human blood groups. This work offers the prospect that human spermatozoal antibodies might be found in unusual biological sources, related only immunologically.

The view of those who know most about the subject is that the development of an effective and acceptable procedure for inducing infertility in humans of both sexes, for fairly closely defined periods of time, is a purely technological problem, the solution of which is mainly a matter of appropriately applied resources.

PROSPECTS

Some of the possibilities for the not so distant and the more remote future, based on scientific achievements already accomplished, have already been mentioned or hinted at. But now comes the much more difficult task—that of predicting the future a jump or more ahead of what might reasonably be expected on the basis of existing knowledge. Here I feel at a real disadvantage, never having laid claim to any powers of prophecy. The daddy, if not the grand-daddy of all the modern science fiction writers—H. G. Wells—was born 100 years ago and he set a standard of accuracy of prediction which was, in some respects at least, almost uncanny; a standard much too high for me to aspire to. Goldzieher (1965), faced with a similar ordeal, said: “The opportunity to speculate publicly on the future course of a given field of knowledge is a rare one indeed. . . . However, when one is actually faced with such an opportunity and looks back to see how well others have fared under the same circumstances, it is a humbling experience to behold the clouded crystal ball of even our most learned and original thinkers. In 1959, for example, there was a major conference on physiologic mechanisms concerned with control of conception, and the proceedings of this conference were summarized by no less eminent men than Carl Hartman and Sir Solly Zuckerman. Among the interesting results of this conference was an inventory of 154 unanswered and presumably fundamental questions. Perhaps the most startling thing about this list in retrospect, is that there is not a single question nor a single approach which pointed to the development, let alone the testing, of intra-uterine contraceptive devices.”

Of course, one can think of many points in the complicated chain of events leading from gametogenesis to conception—or even after, if one is not too squeamish about being labelled an abortionist—where attack by physico-chemical means might result in specific fertility control and which might be suitable for large-scale use. Fortunately, Professor Parkes has already done this for us in his Oliver Bird Lecture of 1961 (Parkes, 1961). However, such an exercise, I suspect, is not very likely to tell us what are going to be the really significant developments in 50, 20 or even 10 years' time. At the Ford Foundation Symposium last May Sir Solly Zuckerman maintained that what reproductive physiology lacked was the kind of break-through that has happened in Physics time and again during the last 30 years. Scarcely anything fundament-

ally new, he believed, had been discovered in that period of time in reproductive physiology. When the real break-through comes, all our prophetic ideas may very likely need drastic revision.

Looking not too far ahead I suggest we shall see—indeed, I hope we shall see—a realization throughout the world of the need for constructive thinking on nationwide family planning; for education and indoctrination of people in the need to prevent too rapid population growth or, in some countries, even its complete curtailment; for instruction in and the provision of existing methods of birth control, and not the least of the most effective methods; and for the provision of adequate financial resources to accomplish this as well as the research which will lead to the later developments. These developments will include modification of existing oral contraceptives, such as continuous low dosage and long-acting, one-pill-a-month regimens; injectables; possibly agents which, by inducing ovulation at a reliably predictable time, would permit the really safe use of the ‘safe period’; anti-implantation agents which could be used after coitus rather than in anticipation of it; pills for the male, including agents which inhibit spermatogenesis, prevent the spermatozoa from moving or from fertilizing without inhibiting spermatogenesis; and long-acting injectables with similar properties. Immunological techniques, used either on the female to inactivate spermatozoa, prevent fertilization or implantation, or on the male to inactivate the germinal epithelium or the spermatozoa, seem certain to be developed to the stage of clinical use, but how widespread an appeal they might have is harder to predict.

The sexual act among humans is successfully performed for procreative purposes on an average perhaps once for every 2000 times it is carried out for sexual gratification. It may, therefore, be argued as Goldzieher (1965) has done, that the most rational form of fertility control would require the participants to “exercise their desire to multiply by a *simple act of free will*”—that is, by taking the antidote to the anti-fertility agent (whatever it might be) which everyone would be having at all times. How the anti-fertility agent would be supplied, and its utilization enforced, is a matter for considerable speculation. I have already referred to the possibility that nutritional factors (like some vitamins) might prove to be essential for reproduction though, unlike known vitamins, without other physiological action. Very likely, inhibitors of such factors could be produced and then the antidote would simply be an antagonist to the inhibitor. If population growth continues without sufficient voluntary checks, a system such as this might well provide responsible governments with the means of licensing reproduction by making the antidote—the ‘fertility pill’ if you like—available only to such persons as, under population programmes, would be permitted to reproduce. But whether any of us would like to consider seriously the introduction of such a system of licensed reproduction in our own lifetimes is questionable. It may have to be considered seriously in our children’s lifetimes.

REFERENCES

- BASKIN, M. J. (1932) Temporary sterilization by the injection of human spermatozoa (a preliminary report). *Am. J. Obstet. Gynec.* **24**, 892.
 BEHRMAN, S. J. (1965) *Immunological aspects of fertility and infertility*. In: Agents Affecting Fertility, p. 47. Eds. C. R. Austin and J. S. Perry. Churchill, London.

- BRADBURY, R. B. & WHITE, D. E. (1954) Estrogens and related substances in plants. *Vitams Horm.* **12**, 207.
- BRUCE, H. M. & PARKES, A. S. (1965) *Pheromones and their role in mammalian fertility*. In: Agents Affecting Fertility, p. 316. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- DRILL, V. A. (1966) *Oral contraceptives*. McGraw-Hill, New York.
- EVERETT, J. W. (1965) *Central neural block to ovulation*. In: Agents Affecting Fertility, p. 244. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- FELTON, H. T., HOELSCHER, E. W. & SWARTZ, D. P. (1965) Evaluation of use of an injectable progestin-estrogen for contraception. *Fert. Steril.* **16**, 665.
- GOLDZIEHER, J. W. (1965) Future approaches to conception control. *Pacific Med. Surg.* **73**, 69.
- GUTTMACHER, A. F. (1964) Intra-uterine contraceptive devices. *J. Reprod. Fert.* **10**, 115.
- HELLER, C. G., FLAGEOLLE, B. Y. & MATSON, L. J. (1963) Histopathology of the human testis as affected by bis (dichloroacetyl) diamines. *Exp. molec. Path.* **2**, 107.
- HUXLEY, J. (1957) *World population*. In: The Human Sum, p. 13. Ed. C. E. Rolph. Heinemann, London.
- JACKSON, H. (1965) *Problems in the chemical control of male fertility*. In: Agents Affecting Fertility, p. 62. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- JACKSON, M. C. N. (1962) Oral contraception in practice. *J. Reprod. Fert.* **6**, 153.
- LUTWAK-MANN, D. & HAY, M. F. (1965) *Maternally transmitted embryotropic agents*. In: Agents Affecting Fertility, p. 261. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- MACLEOD, J. (1965) *Human seminal cytology following the administration of certain antispermaticogenic compounds*. In: Agents Affecting Fertility, p. 93. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- MANN, T. (1957) Biochemical basis of spermicidal activity. *Stud. Fert.* **9**, 3.
- MARTINEZ-MANAUTOU, J., CORTEZ, V., GINER, J., AZNAR, R., CASASOLA, J. & RUDEL, H. W. (1966) Low doses of progestogen as an approach to fertility control. *Fert. Steril.* **17**, 49.
- MATHILL, H. A. & CONKLIN, R. E. (1920) The nutritive properties of milk with special reference to reproduction in the albino rat. *J. biol. Chem.* **44**, 137.
- MAYER, G. (1965) *Tranquillizers and nidation*. In: Agents Affecting Fertility, p. 290. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- MEARS, E. (1965) *Handbook on oral contraception*. Churchill, London.
- MOORE, T. (1965) *Nutritional agents affecting fertility: vitamin E and other nutrients*. In: Agents Affecting Fertility, p. 18. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- NELSON, W. O. & PATANELLI, D. J. (1965) *Chemical control of spermatogenesis*. In: Agents Affecting Fertility, p. 78. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- PAGET, G. E., WALPOLE, A. L. & RICHARDSON, D. N. (1961) Non-steroid inhibitors of pituitary gonadotrophic function. *Nature, Lond.* **192**, 1191.
- PARKES, A. S. (1946) Population. *Lancet*, **i**, 913.
- PARKES, A. S. (1961) Biological control of conception. *J. Reprod. Fert.* **3**, 159.
- PATANELLI, D. J. & NELSON, W. O. (1964) A quantitative study of inhibition and recovery of spermatogenesis. *Recent Prog. Horm. Res.* **20**, 491.
- PINCUS, G. (1955) Some effects of progesterone and related compounds upon reproduction and early development in mammals. *Proc. 5th int. Conf. Planned Parenthood, Tokyo, Japan*, p. 175.
- PINCUS, G. (1959) Fertility control with oral medication. *Stud. Fert.* **10**, 3.
- PINCUS, G. (1965) *The control of fertility*. Academic Press, London.
- PRICE, J. R. (1965) *Antifertility agents of plant origin*. In: Agents Affecting Fertility, p. 3. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- REIFENSTEIN, E. C., PRATT, T. E., HARTZELL, H. A. & SHAFER, W. B. (1965) Artificial menstrual cycles induced in ovulating women by monthly injections of progestogen-estrogen. *Fert. Steril.* **16**, 652.
- RUDEL, H. W., MARTINEZ-MANAUTOU, J. & MAQUEO-TOPETE, M. (1965) The role of progestogens in the hormonal control of fertility. *Fert. Steril.* **16**, 158.
- SHELESNYAK, M. C. (1965) *Inhibition of decidualization*. In: Agents Affecting Fertility, p. 275. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- SIEGEL, I. (1963) Contraception control by long-acting progesterones: preliminary report. *Obstet. Gynec.* **21**, 666.
- SWYER, G. I. M. (1966) The safety of oral contraceptives. *Curr. Med. Drugs*, **6**, 17.
- THOMPSON, J. N., HOWELL, J. M. & PITT, G. A. J. (1965) *Nutritional factors affecting fertility: vitamin A*. In: Agents Affecting Fertility, p. 34. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- TYLER, A. (1960) Approaches to the control of fertility based on immunological phenomena. *J. Reprod. Fert.* **2**, 473.
- WALPOLE, A. L. (1965) *Non-steroidal agents inhibiting gonadotrophic function*. In: Agents Affecting Fertility, p. 159. Eds. C. R. Austin and J. S. Perry. Churchill, London.
- WHO (1966) *Clinical aspects of oral gestogens*. Wld Hlth Org. techn. Rep. Ser. **326**.