PHYSIOLOGICAL CONTROL OF POPULATION GROWTH

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THE heavy consumption of raw materials during the war years of 1939-45, and the phases of shortage that have punctuated the post-war period, have tended to encourage the belief that one day—in the words of the now-famous Paley Report of 1952*—the world will lack the material means to sustain its civilization. The emphasis of the discussion has now begun to shift. To-day we are being increasingly led to believe that modern technology can be relied upon to provide new resources in place of old: nuclear energy for coal; synthetic for natural fibres; and even factory-made food for the food that now grows in the fields. At the same time, however, we are hearing more about the raising of living standards in the under-developed countries, where the bulk of the world's population now lives and multiplies in abject poverty.

The present fear is not that the world's physical resources are in any immediate danger of exhaustion as such, but that plans for the economic growth of 'resource-needy' countries are going to be frustrated by the unrestrained growth of population. This view is the underlying theme of "World Population and Resources", a study recently issued by Political and Economic Planning (*Nature*, January 7, p. 5). It is given further point in the report of the October 1955 meeting of the Consultative Committee for the Colombo Plan (Cmd. 9622), which indicates that population is increasing in the Asian countries far more rapidly than new developments are creating new jobs; and the fear could not be better stated than it has been by the Economic Commission for Asia and the Far East (April 19, 1955) in the words: "despite the strenuous efforts made in the post-war years to increase output and raise levels of living, most countries of the region still found themselves, nearly a decade after the war, with *per capita* real incomes that were either lower than before the war, or barely at pre-war levels". Schemes of economic development may therefore well be nullified if the means are not found for adjusting both sides of the 'population-resources equation' in those 'over-populated' countries where the two are most out of balance.

In these circumstances it is highly encouraging that certain American organizations are making urgent efforts to focus attention on the need to study the problems that are involved in attempts to limit the growth of population. After some preliminary discussions between the Planned Parenthood Federation and the Committee on Reproduction of the National Research Council, the National Academy of Sciences in 1952 convened a meeting out of which emerged a new organization called the Population Council. This was set up with the support of Mr. John D. Rockefeller III; and the next step was the appointment of Dr. Warren O. Nelson, professor of anatomy in the State University of Iowa, as medical director of the Council, with offices in the Rockefeller Institute. Dr. Nelson has made it his business to become acquainted with all work, wherever it may be taking place, that bears on the problem of the control of fertility; and in October 1955 the Council

assisted the International Planned Parenthood Federation to gather together at a meeting in Tokyo a number of economists, social workers and students of reproductive physiology. The result was an up-to-date assessment of the present position about the physiology of birth-control.

Reports about population and economic growth, given by the spokesmen of the resource-needy and impoverished countries of Asia, and of countries like Egypt, all struck the same note. Everywhere population was growing much more quickly than new resources were being created, and nowhere was there any adequate method of checking present rates of reproduction, which were high not because of any increase in fertility, but because of sharp declines in mortality-rates brought about by such events as the elimination of malaria following the discovery of DDT. In Japan the situation had become so serious that abortion had been legalized in an effort to reduce the strain of increasing numbers on an economy which has been struggling desperately to recover from the destruction of war.

The physiological papers dealt with possible means of checking or limiting the actual process of reproduction at one of its many stages, and were mainly concerned to show which lines of research held the greatest promise. In a general review, Dr. Nelson considered the various steps of the process, emphasizing particularly those which appear 'vulnerable', and therefore susceptible to 'designed interference'. For example, one of the more vulnerable stages of spermatogenesis is the meiotic division which primary spermatocytes undergo during the process of chromosomal reduction. The nitrofurans and related compounds can inhibit these changes; but their use in human subjects is contra-indicated because they produce undesirable side effects such as nausea and vomiting. Dr. Nelson's view was, therefore, that research along these lines is no more than "mildly encouraging". Such, too, was his general opinion of current efforts to use steroid hormones, and certain plant extracts (for example, species of the genus *Lithospermum*), to interfere with the action of gonadotrophic hormone.

Dr. S. N. Sanyal, of India, who announced some years ago that there was an anti-fertility substance in the legume *Pisum sativum*, presented a paper in which further claims were made for the anti-fertility properties of *m*-xylohydroquinone, the presumably active substance in the pea. Clinical trials were referred to; but the published results are difficult to assess. The results of animal experiments which Sanyal had reported earlier have not been fully corroborated by research workers either in Great Britain or the United States.

Work on plant extracts was also referred to by Dr. A. S. Parkes, of the National Institute for Medical Research, Great Britain, who in addition directed attention to earlier work on anti-gonadotrophins. Both he and Dr. M. C. Chang, of the Worcester Foundation for Experimental Biology, U.S.A., dealt with the part played in mammalian fertilization by hyaluronidase and hyaluronidase-inhibitors; but again the disappointing conclusion

* Resources for Freedom. In 4 volumes. (Washington, D.C.: Gov. Printing Office, 1952.)

was reached that there was no likely prospect that conception could be controlled by the systematic administration of an inhibitor which could inactivate spermatozoal hyaluronidase—an idea which was once thought to hold considerable promise.

New work on anti-gonadotrophins was reported by Dr. W. O. Maddock. When an animal is injected with gonadotrophins prepared from the tissues of another species, antibodies are formed which are not species specific, so that an animal so treated may become 'immune' to its own gonadotrophins. By proceeding along these lines, Dr. Maddock and his collaborators induced anti-hormone formation in a number of men and women who were receiving daily injections of sheep or hog follicle-stimulating hormone. One month after the cessation of injections, anti-hormone titres were at their maximum, and they usually remained at 'detectable levels' for 2-4 months. Spermatogenesis was apparently unaffected during the first month after treatment; but it was inhibited, as shown by a variety of tests, including testicular biopsies, during the second month. Corresponding signs of the suppression of endogenous gonadotrophin were also observed in the female patients, and in both males and females it was believed that the inhibitory effects of the anti-hormones were more pronounced during succeeding courses of treatment.

The expense, as well as the dependence on medical services of the procedures involved, scarcely encourage one to believe that methods of birth-control deriving from this approach are likely to have any general application in the greater part of the Asiatic world. The experimental results are, however, distinctly encouraging, and it is conceivable that they hold a key to the practical control of reproduction. Another physiological observation which may do the same was outlined by Dr. M. C. Shelesnyak, of the Weizmann Institute of Science in Israel. It has long been known that mechanical irritation of the endometrium during the luteal phase of the oestrous cycle will provoke the formation of decidual cells, and it has also been appreciated that this response can be related to the manner in which a placenta is formed when the endometrium reacts to the presence of an implanting blastocyst. Shelesnyak took as a working hypothesis the idea that a common factor, probably histamine, is always involved when a decidual reaction occurs. This hypothesis proved valid, and further experiment showed that 'histamine antagonists' inhibit the formation of deciduomata. It was then found that a single subcutaneous injection of ergotoxine will interrupt pregnancy in the rat. This physiological observation can be related to the well-established clinical fact that ergot may sometimes act as an abortifacient, although in circumstances which are not clearly understood.

The two communications which excited most attention dealt with the influence of progesterone and related compounds on ovulation, and with the abortifacient effects of a variety of substances described generally as 'anti-metabolites'. The clinical results of the first set of studies remain equivocal, although as Dr. Gregory Pincus, of the Worcester Foundation for Experimental Biology, pointed out, there is no doubt that progesterone can inhibit ovulation in rabbits and apparently, also, in rats. According to his own studies, the indications are that progesterone, when taken by mouth, will also inhibit ovulation in women, as determined by various indirect indices. This view was not, however, shared

by Dr. Massomi Ishikawa, whose clinical trials had failed to provide any indication of the suppression of ovulation, though it was possible that the changes induced by the hormone in the cervical mucus might interfere with the penetration of sperm sufficiently to prevent fertilization, nor by Dr. A. Stone, of New York, who also reported on the negative effects of the oral administration of progesterone. These discouraging observations were, to some extent, counterbalanced by a few observations, also reported by Dr. Pincus, which suggest that 19-nor-17-ethinyl-testosterone and 17-ethinyl oestraeoneolone may be more effective than progesterone in inhibiting ovulation.

The most dramatic story was that of Dr. J. B. Thiersch, of the University of Washington, who discussed the abortifacient action of certain anti-metabolites which are related to various aspects of nucleic acid metabolism, and some of which resemble in their molecular structure naturally-occurring compounds. The investigation began with the observation, made by chance during the course of work on the suppression of cancerous growth, that the folic-acid-antagonist 4-amino-PGA (aminopterin) will destroy the litters of mice, rats and dogs when given in the first trimester of pregnancy. Twelve anti-metabolites were then systematically studied, and nine were found to have a similar effect when given to rats on the seventh or eighth day of gestation. None was able to destroy the whole litter if given before implantation of the embryos, and no compound was effective when given late in gestation. When the drugs failed to destroy all the foetuses, those young which survived usually developed abnormally, and were born in a malformed state. It was also observed that the placentas frequently survived even when the embryos were destroyed, and also that in certain cases the anti-metabolites had toxic effects upon the maternal organism (for example, on the bone-marrow). The most successful abortifacient in rats was azaserine, or azaserine given in combination with 6-mercaptopurine.

Aminopterin has now been given a clinical trial on twenty-six patients in whom pregnancy had to be terminated for medical reasons. The idea was that the anti-metabolite would be tried first, and in case of failure would be followed by operation. In the great majority of patients the drug acted as an effective abortifacient; but in the remainder there were complications (for example, either an abnormal foetus was born, or it was necessary for the surgeon to intervene, in which case an abnormal foetus was found; or general ill-effects occurred in the mother).

It was clear from this, as from all the other physiological papers of the conference, that the practical goal of these urgently needed researches—the discovery of a 'pill' which can be taken by mouth, and the only physiological effect of which would be that of inhibiting the development of the fertilized ovum, or of suppressing ovulation or gametogenesis at will—is so remote from realization that at this stage no one can say how, when or even whether success will ever be achieved. Other communications made it equally obvious that much study will have to be carried out in the field before it will be possible to say how different peoples are likely to react to efforts, officially sponsored or not, to spread a knowledge of birth control. The pressure of population on resources is being felt most acutely in those parts of the world which have never known anything but illiteracy, poverty, overcrowding and squalor. Experi-

once has proved that Western methods of birth control can scarcely be used in such conditions. Moreover, however much some of the people concerned would like to have small families, most of them are either too ignorant or too resigned even to take the trouble to understand the simple facts that are involved in human reproduction. Great efforts have been made in a few areas to overcome these obstacles; but so far with results that are trivial in relation to the size of the problem.

The situation would obviously be transformed if the 'pill' were ever discovered. But the 'pill' would need to be essentially 100 per cent certain, and commercialization would have to be resisted until the most rigorous clinical trials had been carried out, and until it had been shown that there was no danger of any long-term deleterious effects. The Asian peoples are not provided with lavish medical

services, and it would be unthinkable to encourage the use of a drug which was not virtually certain in its action, if its failure meant that a medical man would have to be called in. Moreover, if the drug only affected germ cells or an embryo deleteriously, without destroying them fully, the results could be even more disastrous to the future than the unrestrained growth of population. The West will, therefore, be hurting, not helping, the underdeveloped areas of the world, and would be doing irremediable harm to the good name of Western physiological science, if a 'pill' were launched upon the world before its capacity to satisfy all the desiderata, scientific and social, had been established. But the West will be doing nothing but good if it continues to press on with the kind of physiological research of which the Tokyo meeting provided so useful a résumé.

THE SCIENTIFIC WORK OF BENJAMIN FRANKLIN

By PROF. E. N. da C. ANDRADE, F.R.S.

IN 1746 Benjamin Franklin received from Peter Collinson, of London, a glass tube suitable for carrying out experiments on frictional electricity, with directions as to how to use it*. He set to work on the subject with enthusiasm, writing "For my own part, I never was before engaged in any study that so totally engrossed my attention and my time as this has lately done". He was thus forty years of age (having been born on January 17, N.S., 1706) when he first took up the subject which was to make his name immortal in the world of science, and for seven full years thereafter he was engaged in pioneering experiment, shrewd deduction and simple but penetrating theory. The results of his electrical researches were communicated in a series of letters, beginning in 1747, to Collinson, who was a Fellow of the Royal Society. The publication of these letters as a book in 1751 made Franklin famous throughout Europe and two supplements were issued, the last in 1754. In 1757 Franklin came to England as official representative of the American Colonies, and after that date, although he continued to take a lively, stimulating and practical interest in scientific matters, the pressure of his public duties as a negotiator and statesman made the systematic pursuit of experiment impossible.

One of Franklin's earliest observations, of which he made full use, was on the power of a metal point to discharge an electrified conductor, in his case a large shot insulated by being placed on a clean, dry glass bottle. He generously acknowledged that the first experiment was made by his friend Hopkinson, who, apparently, did nothing to follow it up. If a pointed bodkin was attached to the shot it rapidly lost its charge, as it also did if the bodkin, earthed by being held in the hand, was presented, even at a distance of 8 in., to the shot. If the bodkin was insulated, no such effect took place. He later carried out a similar experiment with a very large charged cylinder made of pasteboard covered with metal foil, when he showed that an insulated man, presenting the point of a needle, became charged. Franklin likewise observed the glow at the point that accom-

panied the discharge. He put forward an explanation of the discharge from a pointed conductor in terms of the attractive force by which the charged body retained its electrified atmosphere: at a point there was a very small attractive surface and a relative inability to hold the charge. These experiments were to lead to the lightning rod.

Very early Franklin carried out experiments in which a man on an insulating base (a block of wax) electrified a glass tube by rubbing and then communicated a charge to another man similarly insulated. By variations of circumstance, including an earth provided by a man standing on the floor, he came to the sound conclusion that, as he put it, electricity was not created by friction, but collected—that there was a separation of electricity which left behind it a corresponding defect. In consequence, he introduced the terms 'positive' and 'negative' electricity, as still used, the electricity of the rubbed glass being positive. His theory was therefore called the 'one-fluid theory'. He also brought into regular use the terms 'non-conductor' and 'conductor' (the term 'conductor' had already been used by Desaguliers) in place of 'electric per se' and 'non-electric' then in general use.

His work on the Leyden jar, which had been discovered in a primitive form by von Kleist in 1745 but brought into general notice by Musschenbroek, of Leyden, in the following year, added clarity to what was a very obscure subject. He showed that the two coatings were oppositely charged and, in particular, that one coating had to be earthed while the other was electrified. He showed the large part played by the glass in the action—in fact, he declared that the whole power of the jar to give a shock lay in the glass. The correct elucidation of the action of the dielectric had to wait for Faraday. While carrying out this work, he simplified the whole matter by making the first plane condenser, of sheets of glass between plates of lead, the so-called Franklin panes, which enabled the coatings and the glass to be readily separated and conjoined. (Franklin has a note to his Letter IV, of 1748, "I have since heard that Mr. Smeaton was the first who made use of panes of glass for this purpose", but I have been unable to trace any record of this work of Smeaton's.)

* With regard to an erroneous date given in Franklin's "Autobiography" and to the general history of Franklin's introduction to the study of electricity, which has been somewhat obscure, see Heathcote, N. H. de V., *Isis*, 46, 29 (1955).