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Abstract
From an address to the Society in November 1968.

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MUTATION RESEARCH AND HUMAN WELFARE

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DOMINANT MUTATIONS

So much has been said and written about genetical risks from radiation that I can be brief. My main concern is to put them into perspective. They certainly should not be played down but they should also not be exaggerated. There is, for example, a widespread belief that children born to irradiated men or women are likely to be in some way abnormal. This is not borne out by observation nor is it expected on theoretical grounds. There are very few abnormal young among the progeny of heavily irradiated mice, and none were found among the children of Japanese parents that had survived exposure to the atom bombs. Theoretically, the type of mutation that would become manifest already in a child of the irradiated person would be a dominant mutation, and such mutations are known to be very rare. It is true that some Japanese women who had been pregnant at the time of the explosions had abnormal children, but these abnormalities were due to direct radiation effects on the foetus, not to effects on the germ cells of the parents. They do not constitute a risk for future generations for, like

the effects of thalidomide or German measles on the embryo, they are not inherited. If, as has been claimed, radiation of the embryo *in utero* increases the risk of infantile leukaemia, this too would not be a genetical damage.

CHROMOSOME BREAKAGE AND NON-DISJUNCTION

What, then, are the risks of radiation that causes so much worry to the geneticist? Chromosome breaks are one of them, although not the most important one. The reason is that chromosome breakage has serious consequences only when it results in a type of translocation that can be inherited and may result in the repeated births of children suffering from a "chromosome disease" like Down's syndrome. However, since a translocation requires the presence of two broken chromosomes in the same cell, it is not often produced by the low radiation doses from fall-out. Much greater is the risk that even these low doses will produce chromosomal disease through non-disjunction, and this has been taken into account in the most recent assessments of radiation hazards.

RECESSIVE MUTATIONS

The most serious radiation damage is due to recessive mutations, i.e. to mutations that become apparent only in homozygous individuals that have inherited the same mutated gene from both parents. Recessive mutations are not only the most frequent ones; they are also produced in direct proportion to the magnitude of the dose, so that there is no lower threshold below which they do not occur. Moreover, the vast majority of them are harmful or even lethal. This is not due to some special malice of Nature. It is simply a consequence of evolution which, in every organism, has selected an array of genes that act together harmoniously in development and that make the organism fit well into its environmental niche. New mutations are much more likely than not to disrupt this nicely adjusted interplay between the genes with each other and with environment. Although mankind certainly could be improved genetically, this cannot be achieved by radiation. For the non-geneticist, it is not easy to grasp the danger of recessive mutations for, by their very nature, these will remain hidden for several and, often, for many generations until affected individuals arise from the coming together of two gametes with the same mutated gene. Moreover, it will almost always be impossible to pinpoint a particular case of, say, phenylketonuria or recessive blindness as being due to a radiation-induced mutation, for radiation does not create new harmful genes, it only increases the frequency of the already known ones. Finally, not all recessive mutations have such drastic effects as blindness or idiocy. Many, probably the majority, are harmful only because they lower some component of fitness, e.g. resistance to infection or degree of intelligence. This can be concluded with a high degree of certainty from experiments on lower organisms, although it would be difficult to prove it for man. There can be little doubt that any increase in mutation frequency will eventually lead to an impairment of human health and happiness. It is our responsibility, especially that of the geneticists and politicians, to see that future generations will not have to pay too heavy a price for the security, health and comfort of the present one.

IRRADIATED FOODSTUFFS

Although it is not easy to arrive at good quantitative estimates of genetical radiation damage, there can be no doubt that such damage exists in all organisms and at all doses. The situation is quite different for another possible type of radiation damage which has recently become a subject of discussion. This is the possibility that foodstuffs may become mutagenic when they have been sterilized by the very high X-ray doses required for this purpose. Already seven years ago, Indian cytologists found chromosome breaks in the cells of plants that had been grown in heavily irradiated fruit juice, sugar solution or potato mash. More recently, the journal "Nature" created quite a stir among the circles concerned by publishing the results of an experiment in which a high frequency of mutations was found in Drosophila flies that had been reared on X-rayed medium. However, repetition of this experiment in many laboratories both here and abroad did not confirm these data: the results were either wholly negative or the increase in mutation frequency was only marginal. There the matter rests at the moment. The whole situation is typical for the uncertainties that beset attempts to generalize findings obtained with chemical mutagens; for it must be realized that, if heavily

irradiated medium should produce mutations, it would do so not through direct transfer of radiation energy but through the production of a chemical mutagen from one of the components of food. Whether such a chemical is formed will depend on the composition of the food; whether it will produce mutations will depend on the digestive and metabolic processes of the organism tested; even in the same organism, different cell types may respond in different ways to the same compound. All these considerations are of importance not only for the special case of irradiated nutrients but for the much more general question whether the exposure to mutagenic influences from chemicals used in industry, medicine, cosmetics, food additions, etc., is not at least as dangerous as the exposure to ionizing radiation from fall-out and X-rays. Indeed, this may well be true, but the uncertainties which I have just mentioned make it exceedingly difficult to arrive at conclusions.

GENETICAL DAMAGE FROM CHEMICALS

Caffeine is a case in question. The situation here is similar to that of irradiated medium. It has been known for a long time that caffeine produces mutations in microorganisms, and chromosome breaks and translocations in plants. It has been calculated that — if human germ cells show the same response — the amount of coffee consumed in the USA or of tea consumed in this country would give cause for serious concern. Experiments on animals, however, seemed to invalidate this conclusion. The results with Drosophila were similar to those obtained with irradiated medium : if there is an effect at all on Drosophila germ cells, it is exceedingly small. The question seemed important enough to test it in experiments on mice, which are much more laborious and expensive than those on Drosophila. Mice were given as much coffee in their drinking water as they could stand without ill effects; in some series, treatment was started already before birth by giving coffee to pregnant females and continuing the treatment on the progeny. Yet neither mutations not translocations were obtained, and for a time this seemed to settle the question. It was re-opened very recently by the finding that caffeine causes chromosome breaks in human cell cultures. It is true that these breaks do not seem to form translocations and therefore are not of the kind that is likely to have genetical consequences, but it is quite possible that this may be different in germ cells. On the other hand, it is also quite possible that no chromosome breaks at all are produced in germ cells. Again, the final conclusion remains doubtful, although the results with human cells certainly warn to caution.

It may seem overcautious to think that the chromosomes in two types of human cell might respond differently to the same mutagen. But this is just what has been found for formaldehyde. When formaldehyde is mixed with the food of Drosophila, it produces high frequencies of mutations in male larvae. Female larvae and adults of either sex are quite immune to its mutagenic action, although — as experiments with isotopically labelled formaldehyde have shown — it penetrates to their gonads. Even in the testes of male larvae, its action is restricted to one particular type of germ cell, the early spermatocyte. I have repeatedly been asked by pig breeders whether mutations may be produced by the practice of feeding breeding animals with skim milk that has been sterilized by formaldehyde. Now it so happens that, many years ago and for an entirely unrelated reason, I have shown that formaldehyde-treated skim milk powder is a good mutagen for Drosophila larvae. But how can one extrapolate from Drosophila germ cells to pig germ cells in the case of a mutagen that distinguishes between Drosophila spermatocytes and Drosophila spermatogonia?

It is this kind of consideration that makes it so very difficult to assess genetical hazards from chemicals. Yet the problem is so important that at present much money and effort is spent on arriving at some conclusions, however tentative. Among the substances for which evidence of genetical effects is being sought is LSD. So far the results have been contradictory : in some experiments, it has produced chromosome breaks in mammalian cells; in others, it has failed to do so.

CANCER THERAPY

There is one group of substances of such high penetration and general mutagenic action that their efficacy in producing mutations also in human germ cells can hardly be doubted. These are alkylating agents used in cancer therapy, e.g. nitrogen mustard. Almost certainly the probability of carrying a new mutation is higher among the progeny of

persons treated with such a compound than among the rest of the population. Since, however, the number of children to which this applies forms a negligibly small part of the whole population, this is not a serious genetical hazard for the population as a whole.

The use of alkylating agents in cancer therapy brings me to the positive applications of mutation research to human welfare. Elimination of cancer cells by chromosome breakage is one of them. It rests on the fact, mentioned before, that chromosome breakage kills only dividing cells and, therefore, acts specifically on malignant cells with their high dvision rate. All the same, it is usually not possible to exclude normal dividing cells, such as epithelial cells, from the irradiated area, and these too are likely to be killed by chromosome breaks. One of the aims of cancer therapy is, therefore, to increase the differential response of normal and malignant cells to radiation. Mutation experiments have given valuable suggestions on this problem. Substances have been found that act as sensitizers for chromosome breakage by radiation, while others act as protectors. If means can be found to introduce such substances selectively into malignant or normal cells, one might make the former more sensitive or the latter more resistant to killing by X-rays. The most powerful and generally effective adjuvant to X-ray effects is oxygen. A given dose of X-rays produces several times as many chromosome breaks in oxic as in anoxic cells. Moreover, only a fraction of the normal oxygen pressure is required to yield full sensitivity to X-rays, so that the sensitivity of normal cells is already at its maximum. Solid tumours, however, often have an anoxic core of highly resistant cells, and this may serve as a source of renewed malignant growth when the more peripheral and better oxygenated cells have been killed. This has led to attempts to improve the treament of solid tumours by radiating patients while they breathe oxygen or are infused intra-arterially with hydrogen peroxide. Neutrons are equally effective chromosome breakers in anoxic as in oxic cells; this is in part responsible for their efficiency in cancer treatment.

PEST CONTROL

Chromosome breakage is also made use of for a very different purpose, the control of noxious insects. You will remember that chromosome breaks or certain types of translocation kill zygotes into which they have been carried by one of the gametes. When males of Drosophila are exposed to very high X-ray doses, they remain able to mate and transmit sperm, but most or all of the eggs fertilized by the sperm fail to hatch. The idea therefore arose that the fertility of wild species might be drastically reduced by catching or rearing males, exposing them to high radiation doses and releasing them again into infected areas. This technique has already had a spectacular success in the case of the screw worm fly, which lays its eggs into the skin of cattle and used to be a great pest in the Southern States of the USA. Nowadays it has practically disappeared from these regions. Occasional invasions from Mexico, where no similar project has been carried out, are combated by the release of sterilized males from aeroplanes near the border. For other species, the technique may have to be modified in order to meet the special physiology or ecology of the insects. Thus in the boll weevil, a cotton pest, the dose of X-rays that kills males is only a little higher than that which sterilizes them, so that X-rays cannot be used for sterilization; chemical mutagens may give better results. For Tsetse flies, a project is now being worked out by which viable, heritable translocations — of the kind that in man causes Down's syndrome — will be introduced into wild populations. While this would not lead to an immediate and drastic reduction in hatchability, it should eventually become a self-maintaining device for producing heritable sterility. Insect control *via* chromosome breakage in spermatozoa is being studied in many countries and discussed at international levels.

IMPROVING THE GENOTYPE

Finally, let me mention the possibility of utilizing induced gene mutations for the benefit of mankind. In work with micro-organisms, this has already been done successfully. Fungi with a higher yield of antibiotics or yeasts with improved baking or brewing qualities can be produced with the aid of mutagens. However, in all these cases, the vast majority of mutations is not of the desired type and many are lethal or at least harmful to the organism. We have seen earlier why this must be so. In micro-organisms, of which huge numbers can be raised easily and cheaply, this wastage is no

impediment to the use of mutagens for improvement. Even in agricultural or ornamental plants, "mutation breeding" is being used quite extensively, especially in inbred strains whose genetic purity one does not wish to destroy by the introduction of desirable genes through crossing. In these cases, too, the loss of, perhaps, a thousand undesirable mutants for the sake of one desirable one may be worth while. For agricultural animals and, even more, for man improvement by induced mutation is out of the question unless treatments can be found which quite specifically produce certain types of mutation. The hope for this to happen is exceedingly slight, at least until the time when we can implant into embryos genes that have been extracted from selected donors or have even been tailor-made in the test-tube. Although this is a distinct possibility for the future, I do not think that it will materialize in mine or even in your lifetime.

DIAGNOSTIC PROBLEM

SET BY JOHN WALLWORK

SUBJECT

Female, age 51.

HISTORY

Pain for nine months of a sharp, gripping nature lasting a few seconds at a time and occurring several times per day. No relation to meals, etc.

ON EXAMINATION

A large mass in the right inguinal fossa was noticed by her General Practitioner on the evening of admission. Some tenderness and guarding was present. Patient was afebrile.

P.V.: Pelvis empty but lower pole of mass palpable high up on right side the mass having a soft consistency.

B.S.: Present.

PREVIOUS HISTORY

Duodenal Ulcer diagnosed several years earlier and treated medically with success.

Barium meal and follow through two weeks before admission showed no abnormality.

INVESTIGATION

Erect abdominal X-ray showed opaque area in right iliac fossa with a few scattered fluid levels in the large bowel.

A. What is the mass in the right iliac fossa?

B. What is the likely cause of the symptoms and signs described?

(Answer on Page 22)

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