is doubling every 3 yr. R. E. Ellis (University of Leeds) has found (ICRP Publication 17) that most individual radionuclide investigations give rise to somatic and genetic doses to patients comparable with those from X-ray examinations, but there are important exceptions and he proposed a set of maximum organ doses (for example, 5 rad for non-pregnant adults) for these tests.

The assessment of the biological effect of small radiation doses was discussed by J. Rotblat (St Bartholomew's Hospital Medical College, London). This is the most difficult step of all, since the effects must be extrapolated from the observed results of irradiation at relatively high dose levels. In the absence of direct evidence, a linear extrapolation is often assumed, but Rotblat thought that this may sometimes underestimate the effect. The evidence from Hiroshima indicates an annual death rate from radiation-induced cancer of all types of $\sim 6/10^6$ adults per rad. For young persons, however, the rate per rad seems to be several times higher, and it is still higher for embryos. For continuing exposure the induction rate depends on the latent period and the number of remaining years of life during which cancer may become manifest. Rotblat concluded that medical uses of radiation in the United Kingdom may lead to an annual cancer rate of 150–750, with perhaps a further 25–600 diseases or abnormalities of genetic origin.

G. Webb (National Radiological Protection Board) discussed the methodology and potential uses of a cost/benefit study in this field. Although a rigorous analysis is not yet feasible, useful results can still be obtained. The overall cost to society is reduced if patient doses are held at the lowest level consistent with a high rate of successful diagnosis and treatments. According to ICRP Report 22 the cost of the detriment associated with 1 mrad is £10–£100. If the mean GSD to the UK population is 20 mrad, the annual cost of the genetic detriment alone is $\text{£}10^7\text{--}10^8$, a significant fraction of the total cost of the National Health Service ($\sim \text{£}2 \times 10^9 \text{ yr}^{-1}$). Webb concluded that the British people can afford to invest a little more each year in the health of future generations.

PHARMACEUTICS

Safety of Contraceptives

from a Correspondent

A MEETING organised by the World Health Organisation was held in Geneva from September 16 to 20 to discuss the use of pharmacological models in the assessment of toxicity and side effects of

fertility regulating agents. The meeting reflected the uncertainty felt by many involved both in the development of new fertility regulating agents and the continued use of presently available ones concerning the assessment and monitoring of toxicity and side effects. A major part of the deliberations was concerned with the extent to which studies performed on animals could be extrapolated to man. The usefulness of the various tests of toxicity and anti-fertility carried out in a number of species was reviewed. To have predictive value these tests should be performed in species in which the reproductive mechanisms, toxic reactions and metabolic disposition of the agents are similar to those in humans. Because of the wide variability of these parameters in different species a number of different species would probably have to be used, an obviously unsatisfactory solution.

If animal models are unsuitable for assessing toxicity, the careful monitoring of subjects using the regulatory agents is of extreme importance and this again raises special problems. These agents are used by normal healthy women over long periods of time and often with little medical supervision. Side effects which occur with a high frequency would be quickly noted but those which occur with a low frequency would be much more difficult to detect. It is these low frequency side effects which are difficult, if not impossible, to detect in animals. As expected, the question of carcinogenicity of presently used hormonal contraceptives provoked much discussion, although those who suggest on theoretical grounds that the oral contraceptives might be carcinogenic in humans have difficulty in finding evidence to support their views. No satisfactory model is presently available to test for carcinogenicity. In considering contraceptive drugs the return of fertility at the end of the treatment period has to be ascertained. The possibility that women might become pregnant while taking, or shortly after having taken, the drug necessitates screening for teratogenic and mutagenic effects.

The requirements for toxicity testing of anti-fertility agents were discussed by representatives of the national drug regulatory agencies with particular consideration to the possibility of standardising many of the requirements on an international basis. These requirements must change in the light of new knowledge. The advantages and disadvantages of methods available for monitoring side effects in humans were also reviewed. The evaluation of reported side effects is complicated by the incidence of placebo reactions and these have not been taken into account in many trials. In addition, variations in response of women of different ethnic

origins to the same contraceptive drug are important. The special requirements for toxicity testing of long acting and of post-coital contraceptives, of spermicides, of various types of intrauterine devices and of the prostaglandins, all of which pose special problems, were also discussed.

It would not be advantageous to increase the amount of animal toxicity testing since this would increase the cost of research and development and, in the opinion of one speaker, "lead to a decreased interest on the part of the pharmaceutical industry to develop new agents. If this were to happen it may ultimately be more disastrous for the survival of large parts of the world population than the limited risk of even serious adverse effects of oral contraceptive preparations". It is hoped that advances in contraceptive technology would lead to a decrease in the amount of toxicity testing that needs to be carried out and hopefully shorten the time between animal testing and preliminary evaluation in humans.

Not unexpectedly, at the end one felt many questions remained unanswered, more research needed to be done, present methodology required improvement and many more discussions were imperative.

CELL BIOLOGY

Control of Proliferation

from a Correspondent

THE sixth meeting of the European Study Group for Cell Proliferation, which was held in Moscow from September 25 to 28 at the Institute of Molecular Biology of the Academy of Sciences of the USSR, took the general title "Molecular Mechanisms and the Control of Cell Proliferation".

Among the invited participants Professor J. M. Mitchison (University of Edinburgh) reviewed the concept of cell cycle markers, within which he included any detectable event which is associated with a localised region of the intermitotic period. Markers fall into three categories: morphological events such as mitosis or abrupt changes in the structure of the cell surface; biochemical events such as the initiation of DNA synthesis or the induction of specific enzymes; transition points at which metabolic inhibitors either begin or cease to be effective. The markers that are available within any one proliferating cell system indicate detectable points in the sequence of gene expression through the cell cycle. In some cases the blocking of one event in this sequence may suppress later events. Other examples can be found in which the sequence of events that make up the "DNA synthesis-division" cycle may to some extent be dissociated