The Pill: A Special Case Within Normal Safeguards Against All Carcinogens

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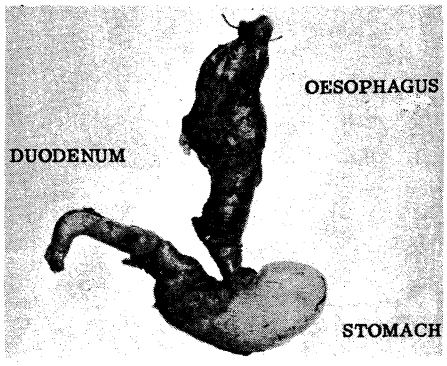
In general, man resembles other animal species in his susceptibility to the induction of cancer by chemical agents: certainly he is not uniquely resistant. However, there are striking differences in sensitivity between species, so the prediction of carcinogenicty for man on the basis of animal experiments is not simple.

Some chemical agents induce cancer in a wide variety of animal species, sometimes in every species examined. The dose required may be minute and far below that required to produce an obvious immediate toxic effect. Certain polycyclic hydrocarbons—including some present in creosote and tar preparations—and many aromatic amines, nitrosamines and alkylating agents come into this category. These agents are so potent as carcinogens that any exposure to them is hazardous.

Carcinogenic drugs

Several drugs useful in the treatment of cancer are potentially carcinogenic: their use is justified because the immediate benefit outweighs the risk that they will induce cancer later. On the other hand, the continued use of creosote and tar preparations is probably not justifiable.

The more serious problem of extrapolation from laboratory to man is presented by agents which are only weakly carcinogenic for animals, agents which induce cancer in only one species despite searching tests in several, agents which induce cancer only when given in doses far in excess of those to which man is likely to be exposed, and agents which induce cancer only when administered to animals by a route which is not used for administration to man. There are substances, for example, which induce local sarcomas when injected into rats and mice, but no tumours at other sites, nor when given by other routes. It has been suggested that in some of these cases the cancers arise not as a result of the chemical nature of the injected material, but because the inoculum remains as a large foreign body at the injection site.



The oesophagus, stomach, and duodenum of a rat. Multiple squamous carcinomas due to exposure to a chemical carcinogen of the nitrosamine type has caused enormous enlargement of the oesophagus.

Certain chemically inert materials induce sarcomas when implanted as solid objects but not in powdered form. Polyvinyl plastic sponge implants induce sarcomas in rats and mice, but have not been used in surgery long enough for us to know if there is a hazard for man. In general, the longer the life span of a species the longer it takes for cancer to develop in response to a specific stimulus.

The practising doctor clearly needs guidance with regard to the use of drugs which may be carcinogenic. A simple rule is never to use potent carcinogens except to save life or where benefit can be expected in patients with a short life expectancy, and to be very careful about giving weakly or potentially carcinogenic drugs in large doses or over long periods.

Action of hormones

The topical question is: Do oral contraceptive preparations come in this latter category? Certainly they may be taken over long periods, but are they carcinogenic? Evidence has been presented to the Committee on Safety of Drugs (see pages 1 and 14) that mestranol, a synthetic oestrogen present in some oral contraceptive perparations, causes severe liver damage and occasionally liver tumours in rats. Liver tumours were seen only in rats given 250 times the equivalent of the normal human dose of mestranol (0.1 mg) daily for 18 months, i.e., about half their life span. Rats given 25 times the human dose for two years showed no liver damage, nor did monkeys given over 60 times the human dose for the same period. For toxic effects other than carcinogenicity, doses less than 1/100th of the minimum which gives evidence of toxicity in the most sensitive animal species, are usually accepted as likely to be safe for man.

Because the action of carcinogens is thought to be irreversible and cumulative, it is argued that no dose can be regarded as safe for man. If this principle had been strictly applied, the use of oral contraceptives, all of which contain an oestrogenic component, would not have been allowable, for there is abundant evidence that oestrogens can induce many different types of cancer in various animal species. The organs affected include pituitary, breast, cervix uteri, testis, kidney, bone, smooth muscle and lymphatic tissue. In nearly all these instances the doses, in terms of oestrogenic activity, were very high compared with physiological levels, and in several cases the carcinogenic effects observed were attributable not to a direct effect of the oestrogen but to a general change in hormonal status mediated via the pituitary.

It is because the carcinogenic action of hormones is probably indirect and dependent on the prior establishment of an unphysiological hormonal status that the rules which apply to carcinogens in general have been relaxed. The hope, if not the claim, of those who advocate "the pill" is that in the doses in which it is given it does no more than alter one state of physiological equilibrium to another—the latter being that which exists in normal pregnancy.

Caution welcomed

Why has the Committee on Safety of Drugs suddenly become concerned about mestranol, which was known at least two years ago to cause liver damage in a small proportion of women taking pills which contain it? Perhaps because it is feared that the damage to the liver is a side-effect unrelated to the hormonal activity. More probably there has been pressure on the Committee to take a closer look at the safety of oral contraceptives and it has used the new report on mestranol as a peg on which to hang its collective hat.

In any case, their decision is welcome—possibly overdue—firstly because it introduces desirable safeguards, and secondly because, by limiting the number of different compounds in use, it makes the task of detecting long-term toxic effects easier. The possibility of hazard is bound to exist until human studies have continued for another 20 or more years. Experiments on animals may point to possible dangers, or provide reasonable confidence in safety, but they cannot remove the possibility of hazard completely.

Despite the new evidence, the risk of serious side effects from the pill appears to be low, whilst the social benefits are, without doubt, considerable.