

together with other chemicals or viruses to produce the complete carcinogenic effect. At present these substances are used as a research tool to try to elucidate carcinogenic mechanisms in animals, and thus they have so far had an academic interest only. Roe would like to see a serious attempt made to relate them to the problem of human cancer, but years of work will be needed before this can be done in any practical way.

It is the duty of experts to advise the legislators on what steps should be taken to reduce environmental contamination and to prevent the introduction of new risks. The latter object seems today less likely to be achieved than ever, because during recent years new carcinogens have been discovered which produce cancer in animals after a single dose or which act in infinitesimal doses and which have no chemical relationship to previously discovered carcinogens. While it is true that a prediction of carcinogenicity can sometimes be made from structural similarity to other known carcinogens, the converse is not true. But this simply means that further search must be made for carcinogens of many varying chemical types, so that eventually a relation between structure and carcinogenic activity may be accurately predicted.

Testing the Pill

Discussions about oral contraceptives, especially their possible side-effects, are apt to arouse strong emotions. This is unfortunate for two reasons. Firstly, it is important that medical men in particular should try to remain scientifically detached. And, secondly, such arguments tend to obscure the one irrefutable fact about oral contraceptives—namely, that except in certain limited therapeutic situations they are drugs taken by healthy women over a long period of time to prevent pregnancy. In addition it has to be borne in mind that at present almost all of them consist of combinations of oestrogens and progestogens, steroid hormones with a chemical similarity which may be reflected in some of their actions but not in others.

Testing for side-effects in man is based on the premise that the drug in question is to be used for a definite and usually relatively short period of time, and in general this practice has been followed in the case of oral contraceptives. The difficulty of interpreting the results is exemplified by the numerous studies that have been carried out on liver function.¹⁻⁴ Rises in serum bilirubin, alkaline phosphatase and aminotransferases, and retention of bromsulphalein have been reported in a proportion of women by some and denied by others. Undoubtedly these differences depend on factors such as the relative insensitivity of the tests employed, dose of the drug, age of the patient, duration of treatment, and so on. But the liver is an adaptable organ, and it may well be that the biochemical changes represent a period of adjustment

rather than actual liver damage. There is no reason, for example, why oral contraceptives should not cause enzyme induction like other drugs. Moreover, the extent to which transient rises in serum enzyme levels reflect liver damage is questionable, and Hans Popper⁵ has warned against the cult of "transaminitis."

Nevertheless, there is no reasonable doubt that a few women do display hepatic sensitivity and react by developing jaundice. It is not yet clear whether this is one extreme of a biochemical function which is always affected in all women, and if so which steroid is responsible. The general consensus is that the oestrogen component is the culprit, a view which is supported by the work of J. Clinch and V. R. Tindall reported at p. 602 of this week's *B.M.J.*, in which they found that stilboestrol, but not megestrol acetate, impaired the ability of the liver to excrete bromsulphalein in postpuerperal women. Yet many progestogens are related to the C17- α -alkyl substituted testosterone, which are also known to cause cholestatic jaundice, and indeed jaundice has been recorded in women taking norethisterone (a progestogen) alone.⁶ It would seem unwise, therefore, to advocate that the oestrogen component should be dropped from oral contraceptives on the basis of rather crude and ill-understood tests of liver function.

But the issue is more fundamental than this. The question that cannot be answered by these or any other tests is what effects oral contraceptives have when taken for twenty years or more. Just as there may be hepatic disturbance in the short term, it is well known that alterations in carbohydrate and fat metabolism and in clotting mechanisms can sometimes be demonstrated. Could these represent the tip of the iceberg of more subtle long-term metabolic adjustments, which might be harmful? Thus in rats it has been found that the long-term administration of norethynodrel impairs uptake of glucose by the brain and increases the lipid content of the aorta, producing quantitative changes in the lipid fractions which resemble those found in atherosclerosis in man.⁷ Other experimental findings have been that progestogens inhibit meiosis in rat ovary⁸ and dog testis.⁹

All these reports emphasize the importance of tests on animals of all drugs which are given to man for a long time; such tests can be done only in animals. The results obtained must obviously be applied to man with caution, and it is encouraging to recall that for some time the Dunlop Committee has insisted¹⁰ on the long-term testing in animals of all new oral contraceptives before they are generally released. We hope that this will now include careful assessment of the separate roles of oestrogens and progestogens.

When to Immunize

It is too much to expect that a perfect immunization schedule against infectious disease can ever be evolved, since accumulated experience is constantly revealing the disadvantages which go to offset the advantages of any particular method. Nevertheless the recommendations¹ on *Immunization against Infectious Disease*, issued by the Department of Health and Social Security in November 1968, should be warmly welcomed by practitioners, since it has now proved possible to discontinue the previous method of presenting alternative

¹ *Immunization against Infectious Disease*. London, Department of Health and Social Security, 1968.

¹ *Brit. med. J.*, 1965, 1, 1391.

² *Brit. med. J.*, 1966, 1, 1499.

³ *Brit. med. J.*, 1967, 4, 499.

⁴ Ockner, R. K., and Davidson, C. S., *New Engl. J. Med.*, 1967, 276, 331.

⁵ Quoted by Schaffner, F., and Klion, F. M., *Ann. Rev. Med.*, 1968, 19, 25.

⁶ Somayaji, B. N., Paton, A., Price, J. H., Harris, A. W., and Flewett, T. H., *Brit. med. J.*, 1968, 2, 281.

⁷ Beaconsfield, P., Abrams, M. E., Ginsburg, J., and Rainsbury, R., *Lancet*, 1968, 2, 832.

⁸ Beaconsfield, P., and Ginsburg, J., *Lancet*, 1968, 1, 592.

⁹ Williams, D. L., Runyan, J. W., and Hagen, A. A., *Nature (Lond.)*, 1968, 220, 1145.

¹⁰ Cahal, D. A., *Brit. med. J.*, 1966, 1, 1540.