Scrotal Carcinoma

SIR,—The incidence of scrotal carcinoma in workers exposed to mineral oil has recently been highlighted by a £10,000 award by Mr. Justice Swanwick.[1] Local inquiries in New South Wales by management, alerted to the possibility of danger of carcinogenesis, prompted me to look into the matter.

In 15 years I have not seen a single case of scrotal carcinoma in New South Wales, despite the fact that many thousands of workers are exposed to mineral oils. Two large insurance companies, which together handle over 50% of the workers' compensation insurance in this State, have never seen a case of scrotal carcinoma. (Squamous carcinoma is quite a common lesion in Australia, involving predominantly those sites exposed to strong sunshine.) Perhaps, in addition to providing impervious aprons for workers exposed to mineral oils, a daily shower at the end of the shift should be mandatory, and underwear and overalls should be laundered frequently. This procedure is voluntarily followed by the vast majority of workers in this State.

Most people would agree that scrotal carcinoma should be an entirely preventable injury.—I am, etc.,

E. O. LONGLEY.

Division of Occupational Health,
Department of Public Health,
Sydney N.S.W.,
Australia.

REFERENCE

1 *The Times*, 5 October 1968.

Tryptophan and Oral Contraceptives

SIR,—Rose[1 2] and Price[3] have shown that women taking oestrogen-progestogen preparations for contraceptive purposes have greatly increased urinary levels of tryptophan metabolites following a 5 g. or 2 g. load. Price measured the spontaneous metabolite excretion in women taking Enovid-E (norethynodrel and mestranol), but did not detect any significant increase in the metabolites measured, although 3-hydroxyanthranilic acid (3HA) was not determined. In two subjects on oral contraceptives Rose and Toseland[4] reported somewhat higher levels of 3HA in acid-hydrolysed urine without loading, but determinations were not carried out before administration of the hormones.

We report here the finding of high levels of 3HA, without tryptophan loading, in two women taking oral contraceptives, and significantly raised levels in two further women studied for the first four months of administration of the hormone, one of whom was investigated for the effect of pyridoxine administration.

Early morning urine specimens were collected from the five subjects taking contraceptive preparations, and 24-hour urine collections as well were made in 12 normal female controls. No tryptophan load was given to any subject. 3HA was extracted from unhydrolysed urine by the method of McMillan[5] and determined fluorimetrically following thin-layer electrophoresis on cellulose.[6] Triplicate determinations were made on each specimen, a standard amount of pure 3HA being added to the third sample. The results were expressed in terms of the subject's creatinine excretion.

Urinary levels of 3HA in the controls aged 22–50[7] ranged from 0·10–1·00 mg./g. creatinine. These results agree with those obtained by Benassi,[8] but are slightly lower than those of Schievelbein.[9] In three women aged 21–26, with no evidence of renal disease, who had already been taking oral contraceptives for 3–15 months, the urinary 3HA was 1·5, 0·2, and 1·3 mg./g. creatinine respectively. In two further women aged 18 and 25 studied progressively the values obtained were as follows:

In mg3HA/g. creatine

Prior to taking Hormone	After 4 Weeks on Hormone	After 4 Months on Hormone	At 4 Months after 5 Days on Pyridoxine 20 mg./day
0·26 0·15	0·52 —	3·14 0·75	0·40 —

Three significant facts emerge from this finding: (i) increased values of 3HA can be detected without tryptophan loading; (ii) the increase rises progressively with the duration of the administration of oestrogen-progestogen compounds; and that (iii) the increase is apparently reversed in a subject given pyridoxine supplements.

The last finding adds further support to the suggestion of Rose[2] and Heeley[10] that pyridoxine may influence the metabolic fate of 3HA in the tryptophan-niacin pathway. These cases were found in a larger group of healthy young women, used as controls, in a study of the increased excretion[5] of 3HA in rheumatoid arthritis. In this context it is interesting to read the report from Ann Arbor[11] of the apparent increase in the incidence of rheumatoid symptoms associated with the use of oral contraceptives. We realize, of course, that two subjects do not provide sufficient evidence to test this hypothesis, and the work is therefor being extended to cover a wider range of steroid hormones used in conception control and to study further the effects of pyridoxine supplements.—We are, etc.,

P. A. TOSELAND.

Department of Clinical Pathology,
Guy's Hospital Medical School,
London S.E.1.

SARAH PRICE.

Department of Medicine,
Guy's Hospital Medical School,
London S.E.1.

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Toxicity of Carbon Tetrachloride

SIR,—I was interested to read Dr. R. J. Weir's memorandum on carbon tetrachloride poisoning (22 February, p. 487). We have recently confirmed the view that the toxicity of carbon tetrachloride (CCl_4) is dependent upon the activity of the hepatic drug-metabolizing enzymes.[1] These enzymes are responsible for the breakdown of many substrates such as drugs and steroids, and their activity can be altered by dietary and nutritional factors, hormonal changes in the body, and the ingestion of foreign chemicals.[2]

We have developed a convenient method of increasing drug-metabolizing activity in rats by administering oral phenobarbitone in the drinking-water.[3] Although the daily dose of phenobarbitone exceeds 100 mg./kg., doses which can be related to those taken by humans therapeutically cause a significant increase in activity.

Pretreatment of rats with phenobarbitone causes the median lethal dose (LD_{50}) of CCl_4 to fall from 3·6 ml./kg. to 0·5 ml./kg. 0·25 ml. CCl_4/kg. produces severe liver damage in phenobarbitone pretreated rats as shown by high liver fat and water content and high plasma isocitrate dehydrogenase and bilirubin levels. This dose of CCl_4 produces only slight damage in control rats. The amount of CCl_4 metabolized in the first six hours after administration of 0·25 ml. CCl_4/kg. to phenobarbitone pretreated rats is the same as that of control rats given a tenfold larger dose. Previous work has shown that rats fed on a protein-depleted diet are much less susceptible to CCl_4 poisoning,[4] and this has been shown to be due to a very low level of hepatic drug-metabolizing enzyme.[5] These facts indicate that the toxicity of CCl_4 is closely linked to its metabolism.

Administration of phenobarbitone to man has been shown to produce an increase in the rate of metabolism of phenylbutazone.[6] Although, for obvious reasons, no work has been done on the metabolism of CCl_4 in man, it is likely that its metabolism will also be accelerated leading to increased toxicity.

It cannot be overemphasized that carbon tetrachloride is a highly toxic substance in any circumstance, and that individuals who are on barbiturate therapy may have a greatly increased susceptibility.—I am, etc.,

R. C. GARNER.

University College Hospital
Medical School,,
London W.C.1.

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Economics of Dialysis

SIR,—The small but expanding group of doctors and nurses who man haemodialysis units throughout the country struggle daily with deficiencies of equipment, accommodation, and trained staff to the extent that these difficulties have become facts of life rather than limits. It is the time that it takes to dialyse a patient that is the real limitation to expansion of work, and the 14 hours' dialysis applied by a Kiil kidney is a full day's work for an installed mass of equipment worth probably £2,000. It also incurs the uncomfortable business of building the Kiil kidney and providing accommodation and staff for this wet performance. Money is important, and it is said that presterilized disposable coils are more expensive than Kiil boards. This has been debated too long and without a real, true costing on a basis of convenience, safety, and speed as well as cash.

The Capon-Heaton mini-coil (14 hours dialysis), costs £7; the Baxter "Ultraflo" coil costs £9 to dialyse adequately in seven hours. Our estimate of the cost of the 14 hours' dialysis, using the Kiil kidney, is a minimum of £5 each time and it is wet, messy, and often frustrating. From the bacterial point of view, the Kiil board