Letters to the Editor

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Coal Tar Constituents and Cancer

THE nature of the cancer-producing constituent (or constituents) of coal tar has been under investigation in this and other laboratories for some years past, but hitherto no known constituent of tar has been found to have definite cancer-producing properties, and no new carcinogenic constituent has been isolated. The isolation has now been accomplished by concentrating active fractions of coal-tar pitch, making use of the method of fluorescence spectroscopy introduced here by W. V. Mayneord. This brought to light a spectrum which was found to be common to many carcinogenic mixtures.¹ The methods adopted have included fractional distillation, solvent extraction, and crystallisation of picrates and of the products of their decomposition with alkali.

In this way a very active carcinogenic hydrocarbon has been obtained, which in the pure state has the typical fluorescence spectrum to which reference has been made above. For reasons which cannot be detailed here, we formed the opinion that this hydrocarbon was possibly 1:2-benzpyrene. This compound was unknown, but has now been synthesised here from pyrene by way of β -1-pyrenoylpropionic acid, γ -1-pyrenylbutyric acid, and 4'-keto-1': 2': 3': 4'-tetrahydro-1: 2-benzpyrene. The synthetic sample of 1:2-benzpyrene produced cancers of the skin in mice just as rapidly as the material isolated from pitch.

The tumours appeared, so far as can be judged from the limited number of experiments on mice yet carried out, in approximately half the time required for tumour production by 1:2:5:6-dibenzanthracene, so that 1:2-benzpyrene is much the most active carcinogenic hydrocarbon yet known. We do not claim that this is the only carcinogenic compound present in coal tar. The relationship of this new hydrocarbon to 1:2-benzanthracene, the parent substance of the group of cancer-producing hydrocarbons already described,² is shown by its structural formula, the benzantracene ring-system being indicated by heavy lines:

In addition, we have also isolated from coal-tar pitch the other two hydrocarbons, $C_{20}H_{12}$, composed entirely of benzene rings; namely, perylene and 4:5-benzpyrene. The identification of the latter hydrocarbon was effected by synthesis. Moreover, we have isolated 1:2-benzanthracene from the chrysene fraction of coal-tar. None of these four hydrocarbons had previously been recognised as a coal-tar constituent. A more complete account of these experiments is being prepared for publication.

No. 3294, Vol. 130]

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¹ Hieger, *Biochem. J.*, **24**, 505; 1930.

² Cook, Hieger, Kennaway and Mayneord, *Proc. Roy. Soc., B*, **111**, 455; 1932.

Tribulosis and Methæmoglobinæmia in South African Sheep

In the investigation of the disease 'tribulosis' or 'geeldikkop' (literally, 'yellow-thick-head'), which causes heavy mortality among sheep in the Karroo area of South Africa, it was observed by one of us¹ that death from methæmoglobinæmia followed administration of the press juice of the plants held responsible for the causation of the disease. Animals grazing upon different *Tribulus* species (*Zygophyllaceæ*) at certain periods of the year (summer months) evince a marked photosensitivity accompanied by more or less intense icterus. The swellings of the lips, ears and head, those parts least protected from the sun's rays, are followed by necrosis and mummification of these parts, which may be so intense that the animal is quite unable to eat or drink. Death follows from inanition, toxæmia and jaundice.

Methæmoglobinæmia has never been recorded as a clinical symptom. With the exception of the jaundice, the clinical picture very closely simulates that produced by experimental *Hypericum* or hæmatoporphyrin sensitisation.²

The rôle of the plants mentioned in causing the disease has been established by feeding tests carried out at the scene of an outbreak, but so far no clue as to the nature of the toxic substance responsible has been obtained, neither has the disease been produced experimentally outside the areas in which it normally occurs. Outbreaks are very spasmodic, even capricious, in appearance. It is felt by us that a certain set of physiological conditions is necessary, both of the plant and of the animal, for the characteristic syndrome to develop.

In testing the toxicity of *Tribulus* plants at Onderstepoort, death invariably resulted from methæmoglobinæmia within 3-4 hours of dosing (by stomach tube) with the freshly expressed juice of the green plant, or water extracts of the dried, powdered material. Although the symptoms of such poisoning differed markedly from those of the disease as it is seen in the field, it was decided to attempt the isolation of the responsible substance.

We have succeeded in proving that the formation of methæmoglobinæmia is due to nitrite, not present as such in the plant, but formed from nitrate by an extremely active reducing system.

Determinations of nitrate content by the method of Strowd³ (except that extracts were made with boiling water), showed that our dried, powdered samples of *Tribulus* plants from various localities contained between 3.2 and 2.2 per cent, reckoned as KNO_3 , on the dry weight basis. Since conversion of nitrate to nitrite and reaction of this with amino bodies, etc., takes place during the drying process, the actual amount of nitrate in the fresh plant is