CANCER-PRODUCING CHEMICAL COMPOUNDS

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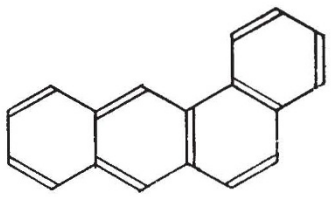
IN the last resort, the degree of importance which is attached to the carcinogenic substances depends upon whether such compounds are concerned in the etiology of 'spontaneous' human cancer. Perhaps closely bound up with this question is another unsolved problem of outstanding importance, namely, the manner in which these compounds bring about a transformation of normal cells into malignant cells. At least until answers are forthcoming to these questions, the carcinogenic compounds will continue to furnish useful material for the experimental study of cancer. Industrial cancer, in its various forms, has stimulated the researches which have brought to light the cancer-producing properties of the various carcinogenic agents, and in the preparation of the present brief survey of these agents regard has been paid to the correlation of the various forms of industrial cancer with their causative compounds.

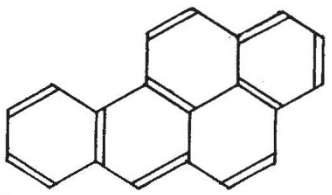
In the earlier work on the carcinogenic properties of substances the skin of the mouse was usually employed as the test object. This was due to a number of reasons. Results could be expected comparatively rapidly; the ear of the rabbit, which had been first used, was less satisfactory in this respect. Moreover, the modes of application of the substances under examination were considerably restricted by the toxic and inflammatory properties of the crude mixtures which it was necessary to use. Many of these difficulties have been resolved by the availability of pure chemical compounds of high carcinogenic potency, and in recent years new techniques of administration have been developed, so that malignant tumours have been induced in a large number of different tissues, and in several different species. One outcome of these and other studies has been the revelation that, in certain strains of animal, tumours of a particular organ are apt to occur spontaneously. Thus, some strains of mice show a high incidence of mammary carcinoma; other strains show a high incidence of lung cancer; and there is at least one strain of mice in which liver-cell cancer (hepatoma) is apt to arise spontaneously. These findings indicate the caution that must be used in interpreting the results when cancers of such organs are found in experimental animals, especially when the tumours arise at sites other than that of application of the carcinogenic agent. Yet even so, tumours clearly attributable to the treatment have been found, usually at the site of application, in a variety of tissues of animals treated with carcinogenic compounds. In this respect the most versatile substances so far found are contained in the group of polycyclic hydrocarbons, mostly related to 1 : 2-benzanthracene (I), in which substituents are present at certain well-defined positions in the molecule. With these compounds malignant tumours have been obtained, usually in mice and rats, in such tissues as the skin, the subcutaneous tissues, the peritoneal cavity, the liver, the prostate, the forestomach, the brain, and the spleen; and this list is not exhaustive. Less widespread in their effect are members of other classes of compounds, where usually carcinogenic action has not been shown except in a single organ. In this connexion it needs to be borne in mind that these substances have not usually been so widely investigated as the polycyclic hydrocarbon class.

The earliest form of industrial cancer, recognized as such in the latter part of the eighteenth century, was the cancer of the scrotum to which chimney sweeps were specially liable. This was caused by soot, and the pursuit of the clue so provided culminated eventually in the isolation from coal tar of the individual compound responsible. This is 3 : 4-benzpyrene (II), an aromatic hydrocarbon, the relationship of which to 1 : 2-benzanthracene (I) is apparent from the formulæ. 3 : 4-Benzpyrene is undoubtedly the principal cancer-producing constituent of coal tar. It has a high boiling point, and hence is present to an appreciable extent only in the highest boiling fractions of the tar. There are grounds for inferring that this or a similar compound is responsible for the carcinogenic properties shown to varying degrees by some of the mineral lubricating oils. Prolonged contact with industrial products of these types is now recognized as being fraught with danger, and the use of suitable precautions should lead to diminution if not to eradication of the form of industrial cancer which they are liable to cause.

The widespread use of tar in road surfaces, and the publication of statistics which appear to show that cancer of the lung is increasing at an alarming rate, have led to the suggestion that tarred road dust may be partly responsible for this increase. This suggestion has been tested experimentally;



(I)



(II)

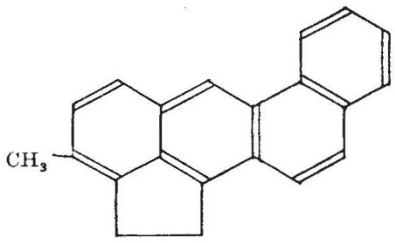
but although an increase in lung cancer was found in mice breathing air impregnated with road dust, this increase was not wholly related to the presence of tar in the dust, and the results of the experiments do not directly implicate such an agent in the increase of the human disease. Furthermore, it is considered by many authorities that the recorded increase in lung cancer is largely accounted for by improved methods of diagnosis. Unconvincing attempts have also been made to implicate pollution of town air by soot, exhaust fumes, etc., and also tobacco smoking in the increase of lung cancer. However, the knowledge that the agencies in question may be, and sometimes are, associated with carcinogenic substances, does not allow such speculations to be too lightly dismissed.

The carcinogenic activity of 3 : 4-benzpyrene is of a high order, inasmuch as tumours arise in a large proportion of the treated animals, in a relatively short time. A somewhat greater potency is shown by 20-methylcholanthrene (III), a hydrocarbon first obtained by chemical transformation of the bile acids, and later indirectly from cholesterol. Other hydrocarbons of similar structure have similar high activity. An altogether higher order of activity, judged by the criterion of shortness of the latent period in the induction of skin tumours in mice, has recently been found in a small group of hydrocarbons typified by 9 : 10-dimethyl-1 : 2-benzanthracene (IV). These compounds, which are characterized by the presence of methyl groups in the positions shown, have in mice skin given tumours which frequently made their appearance within a month of the first application.

It will be observed that the carcinogenic hydrocarbons thus far mentioned are all derived from 1 : 2-benzanthracene (I). A very considerable number of other carcinogenic derivatives of 1 : 2-benzanthracene is now known. These are purely synthetic compounds, not known to be associated with either industrial or naturally occurring products. Their chief interest lies in the large number of closely related compounds which have been shown to have such biological activity, and in the generalizations which it has been possible to arrive at regarding the correlation of carcinogenic activity with molecular structure and with other properties.

The benzanthracene group is not the only group of polycyclic hydrocarbons with carcinogenic properties. Feeble activity is shown by 3 : 4-benzphenanthrene (V), and systematic examination of homologues and derivatives now in progress is pointing to the conclusion that much enhanced activity is shown when suitable substituents are introduced into positions 1 and 2, but not into other positions of the molecule. Before 3 : 4-benzpyrene had been isolated from coal tar, it had been claimed erroneously that chrysene, also a coal tar constituent, had carcinogenic properties. This error appeared to be due to the incomplete purification of chrysene of coal tar origin. These and other circumstances have caused some attention to be devoted to chrysene derivatives, and a number of chrysene homologues, selected in a haphazard way, have been synthesized and found inactive when tested biologically. More recently a consideration of the structural relationship among the carcinogenic derivatives of 1 : 2-benzanthracene and 3 : 4-benzphenanthrene led C. L. Hewett (*J. Chem. Soc.*, in the press) to synthesize 1 : 2-dimethylchrysene (VI), and this hydrocarbon has been found to have definite carcinogenic activity when tested by application to the skin of mice.

For many years it has been recognized that the operatives engaged in certain sections of the



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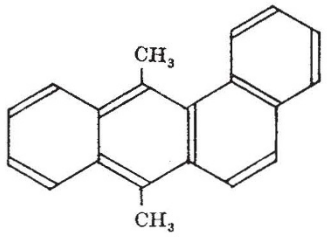
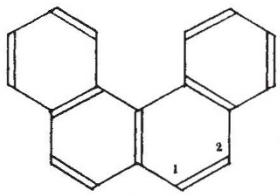


(IV)

chemical industry, and especially in the manufacture of dyestuffs, are more liable to cancer of the urinary bladder than is the general population. This form of cancer was long known as 'aniline cancer', and the prevailing opinion for many years has been that it is due to absorption of nitrogenous bases such as benzidine and the naphthylamines, especially β-naphthylamine. Until recently the evidence was purely circumstantial, and many unsuccessful attempts have been made to induce experimental tumours with these bases. Some two years ago, however, the production of bladder tumours in dogs given, subcutaneously and orally, large daily doses of a high grade of commercial β-naphthylamine was reported by American workers. It was doubtless the prevalence of this dye-workers' cancer, coupled with the known cell-



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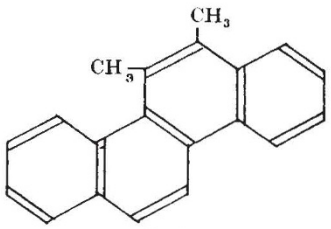
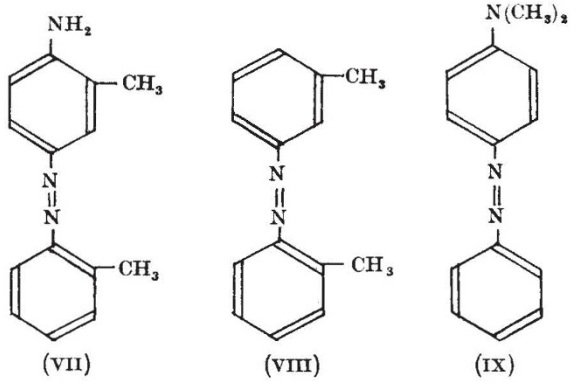


(VI)

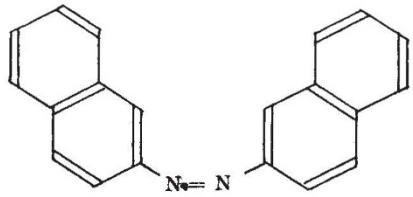
proliferating properties of Biebrich Scarlet *R*, which led to Japanese researches which have shown that a number of relatively simple azo compounds have carcinogenic properties. The principal active compounds which have been revealed by this work are 4′-amino-2 : 3′-azotoluene (VII), which gives liver-cell tumours when fed to rats and mice, 2 : 3′-azotoluene (VIII), which gave malignant tumours of the urinary bladder in rats, and *p*-dimethylaminoazobenzene (IX), which is mainly carcinogenic towards the liver.

In view of the possibility that contaminants of the naphthylamines might be responsible for the dye-workers' cancer, a number of possible transformation products have been administered to rats and mice in the research laboratories of the Royal Cancer Hospital, London. Mice treated with 2 : 2′-azonaphthalene (X) by application to the skin, or by subcutaneous injection, or by feeding, have developed many liver growths, some of them liver-cell carcinomas, but most were of a cholangiomatous type. Similar tumours were obtained with 2 : 2′-diamino-1 : 1′-dinaphthyl (XI), a product



which arises easily by intramolecular change of the dihydride of (X), and also with 3 : 4 : 5 : 6-dibenzcarbazole (XII), which is formed by deamination of (XI). There is thus the possibility that the biological effects of this series of compounds are due to a common metabolite, and it is worth noting that the final product of the series (XII) has a structural resemblance to the carcinogenic polycyclic hydrocarbons.

One of the azo dyes found to be carcinogenic to the liver by the Japanese workers, namely, *p*-dimethylaminoazobenzene (IX), was formerly used as a food colouring matter under the name of 'butter yellow' and has also been used in dyeing leather. Fortunately, its use in these respects appears now to be obsolete. In Great Britain the range of permitted food colouring matter is now very limited. With the co-operation of the Government Chemist, tests have been carried out in which



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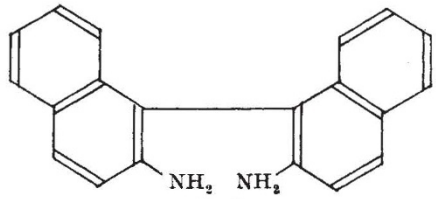

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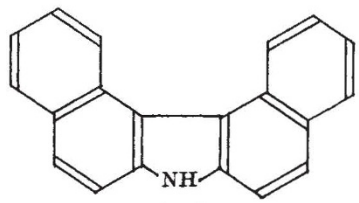

(XII)

relatively large amounts of a selection of these permitted dyes were regularly administered with the food to rats and mice. The compounds chosen were azo compounds bearing some structural resemblance to the azo compounds discussed in the present article. They are mostly water-soluble sulphonates, a circumstance which facilitates rapid elimination. In a few of the mice stomach tumours were obtained; but it is by no means certain that these were due to the dyes.

Existing knowledge of the structures of the various carcinogenic compounds and of the conditions under which they may be formed has led to various speculations regarding the possibility of such substances being present in human food. Some workers have recorded the production of skin tumours by heated fats and by tars prepared by heating coffee. It has been claimed also that wheat-germ oil prepared by a special extraction process produces sarcomatous tumours in rats. This claim has not thus far received independent confirmation, and at the present time there is no evidence that cancer of the internal organs is due to specific dietary constituents. However, it is evident that such lines of inquiry should be pursued.

A puzzling and in some ways disconcerting feature of the carcinogenic agents now known is their variety and their apparent lack of correlation. It may be recalled that cancer may be induced not only by the classes of compound reviewed in this article, but also by several other agencies. The malignant tumours which arise in consequence of exposure to ultra-violet light, X-rays, and radioactive substances may well be due to the production of carcinogenic compounds from normal constituents of the tissues.

There is, however, no evidence that the radiations exert their influence in this indirect manner. Cancer of the skin occurs in persons taking arsenic by mouth over long periods, and has also been found in workmen engaged in handling arsenical sheep dips. Teratoma of the testis in fowls can be induced by injection of zinc salts at the season of the year when the testis is actively secreting androgenic hormone. At other times also this type of growth may be produced if gonadotropic hormone is simultaneously administered, so that at least two factors seem to be involved.

Thus, in carcinogenesis we have a biological phenomenon which may be attributed to a variety of different substances and agencies. This is by no means unique, for the same is true of other biological phenomena; but it is a circumstance which adds to the difficulty of interpreting the biological properties of the carcinogenic compounds and in estimating their ultimate significance.

OBITUARIES

Prof. Sydney J. Hickson, F.R.S.

BY the death of Prof. Sydney J. Hickson on February 6 at Cambridge, British zoology loses one of its most distinguished professors. He was born in 1859, and was at Manchester from 1894 until 1926, during which he was identified with every aspect of the development of the University of Manchester. At the same time he annually contributed to the store of knowledge not only by his special researches on the soft corals, but also by investigations relating to water supplies, hospital sanitation, poultry and many local questions.

Hickson was the youngest of a family of nine, most of the older boys of whom were absorbed into the family manufacture of boots and shoes, then situated within the City of London. His parents were of Unitarian stock with advanced social views, and among their visitors he recalled Mrs. Besant, Charles Bradlaugh, Auberon Herbert, Charles Voysey and G. T. Holyoake, the last person in England to be sent to prison for blasphemy. This early intercourse left a permanent impression, and Hickson always remained an advanced Whig in public affairs, taking a particular interest in the Land Values League of Manchester. In contrast he was an 'out and out' Tory in his ordinary life, and a friend recalls his top-hatted, athletic figure on its morning walk from Withington to the laboratory.

Hickson's early education was at the Mansion Grammar School at Leatherhead, a beautiful old domain on the River Mole. Here he followed his brothers and acquired a taste for Nature, as Ray Lankester had done at the same school. In 1893 he entered University College School, passing on to the College in 1876, where he was so enthralled by Lankester's lectures—the courses commenced at 8 a.m.—that the following year he was Gold Medallist. Then he went on to "Barts", but he found conditions "indescribable and terrifying", Klein's course on histology being to him their one redeeming feature. Lankester advised Cambridge, and there in the laboratories of Michael Foster and F. M. Balfour he found his vocation and made many friends, Sedgwick, Haddon, Bullen, Caldwell, Threlfall and many others. He obtained a first class in the Tripos of 1881; but he had already, by dissecting, teasing and the use of the sliding microtome, begun his laborious studies of the eyes of Pecten and Spondylus; each section was removed and mounted separately by hand, for Threlfall had not yet made his automatic microtome. Similar technique was also employed for his now classical research on "The Eye and Optic Tract of Insects", 1885.