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OCCUPATIONAL CARCINOGENESIS

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Interest in this subject rests not only on the obvious implications for industrial hygiene and safety but also on the suspicion that there may be many more carcinogenic influences at work than are at present known or suspected, and that non-occupational cancer may also be related to some exogenous causes. Moreover, the recognition of occupational carcinogens must lead to fruitful experimental study not only to sustain the clinical or statistical contention but to seek some underlying unity among the diverse materials or their effects which can evoke the cellular neoplastic reaction. The agreement that a particular material is an occupational carcinogen requires ideally that it shall be shown, by long collection and analysis of occupational and clinical data, that the incidence of the disease among those exposed to the suspected agent so far exceeds the incidence of its non-occupational counterpart that there can be no reasonable doubt of the nature of the carcinogenic agent or its precursor, or of the process in which it resides. When, as is usually the case, it is necessary to build on retrospective data, death-certificates, befogged occupational histories, mobility of workers, multiple exposures, poor or no factory records and inadequate information on past environmental conditions, the difficulties are much increased in reaching any clear conclusions. The present brief consideration will be restricted to those materials which were more or less summarily discussed in volume 3 of Merewether's *Industrial medicine and hygiene* (Goldblatt & Goldblatt, 1956).

1. Asbestos

The peculiar association of carcinoma of the lung with asbestosis, first presented by Merewether (1949) and Gloyne (1936, 1951) with strongly suggestive statistics, finds confirmation in the Annual Report of the Chief Inspector of Factories and Workshops for 1955. For the period 1924–55, 22% of 222 men and 12% of 143 women showed combined asbestosis and lung cancer, indicating a rising incidence of the association as compared with that reported in 1947 and in 1954. So high an association does not occur in silicosis (see Goldblatt & Goldblatt, 1956; Gloyne, 1951; Meiklejohn, 1956). Werber (1952) states that carcinoma of the lung follows epithelial metaplasia in 7–17% of cases of asbestosis, with a latent period of 1½–20 years. Doll (1955) analysed the post-mortem findings in 105 workers in a single large asbestos works, whose deaths occurred consecutively. Of these 75 had asbestosis, and of them 15 had associated lung cancer, whereas of the remaining 30 without asbestosis 3 had the tumour. All the 15 with asbestosis cancer had worked for periods of 9–23 years in the industry before 1933, when the 1931 Asbestos Industry Regulations became effective in the factory, but the association was not recorded in any person entering the industry for the first time between 1923 and 1953. In the mortality data of 113 men who had worked at least 20 years in the factory, Doll found 11 death-certificates with asbestosis and lung cancer, whereas there were none of lung cancer without asbestosis. This incidence is some ten times that expected from the England and Wales mortality data for lung cancer. Observations published over 20 years ago in South Africa by the Miners' Phthisis Medical Bureau, cited by Doll (1953), showed that the incidence of primary lung cancer in silicotic miners was 0.7%, for non-silicotic miners 0.7% and for European male surface workers 0.9%. Agreement on the relation between asbestosis and lung cancer was reached at the international Symposium on the Endemiology of Lung Cancer (1953).

Wyers (1949) reported the cell types to be oat cell, columnar and endothelial (pleura), the first two being the most frequent. According to Hunter (1955) the carcinoma usually appears many years after exposure to asbestos has ceased. This is not borne out by the data in Doll's paper, where the periods from last exposure to death in the 15 cases with the combined diseases are given as less than 1 year in 6 cases, 1 year in 3, 3 years in 3, 8 years in 2 and 13 years in one.

The induction time is probably very long, inasmuch as the tumours seem always to be of high malignancy, with only a short time between commencement of tumour process and death.

As to cause and mechanism, Meiklejohn (1956) and Chiurco (1956) speak of irritant factors, whereas Bonser, Faulds & Stewart (1955) suggest that the common factor in the exposure of the asbestos textile worker and the haematite miner (see section 4 below) is silica and that in both types of lung cancer the fibrosis precedes the malignant process. They conceive the fibrous asbestos (probably chrysotile) and the iron oxide as modifying the action of silica, or of the fibrotic process, so that silica acts more as a carcinogen and less as a fibrosing agent.

No experimental evidence is available that asbestos in any form (small or large fibres) can act as a carcinogen, although peribronchiolar fibrosis has been demonstrated in rabbits by King, Clegg & Rae (1946) and others; but if the asbestos is fused and ground no fibrosis is induced even after long inhalation. Physical form and flexibility are evidently determinants, since peribronchiolar fibrosis can be induced also by brucite which is a native, crystalline form of $Mg(OH)_2$ and contains only some 0.9% SiO_2 as silicate (chrysotile contains over 40% SiO_2 as silicate).

It must be noted, also, that three of Doll's patients who had the first exposure after 1939 and total exposures of 2, 9 and 7 years, showed no asbestosis and died in 2, 12 and 11 years after the first exposure, from carcinoma of the lung. Knox & Beattie (1954a) would explain such cases as not having had sufficient time to develop asbestosis, and that the neoplastic change, induced by asbestos as such, by asbestosis

bodies or by some endogenous agents, including decomposition or solution products of asbestosis bodies, may precede the changes necessary in the inhaled material to induce asbestosis proper. In another communication, Knox & Beattie (1954b) confirmed Gloyne's view that with time the number and size of asbestosis bodies and fibres in the lungs diminished, an opinion held previously by the pathologist M. J. Stewart of Leeds. Stewart regarded the fibres and asbestosis bodies as being gradually dissolved, the products inducing the lesions which survive the fibres. Evidence supporting these views as to solubility was obtained with electron microscopy by Champeix & Bouteville (1950).

Knox (1955) is, on the whole, of the opinion that the epithelial changes leading to carcinoma arise from: (i) chronic irritation leading to increased thickening and compression of the alveolar walls and (ii) subsequent slow disintegration of the asbestosis bodies with liberation of something which, acting on the already abnormal epithelium, induces malignancy. The views of Chiurco (1956) apply here as elsewhere, to the effect that, in the interpretation of the occupational precancer and tumour states, it is very important to consider the soil prepared for cancer; the aetiology is multiple, syncarcinogenesis and cocarcinogenesis together with a whole constellation of factors, co-factors and co-causes; these bring about and favour a restless terrain, labile, unstable, dynamic, on which will develop cancerization by the release of factor X.

2. Chromium

In the case of chromium we have an element of which particular compounds are either poisonous or induce chronic ulceration, dermatitis or caustic effects. Chrome holes, nasal septum perforation, chrome dermatitis and chrome burns are not followed by neoplastic change (cf. Legge, 1922). But from 1935 onwards, Continental and American observers presented evidence in support of a lung carcinogen in the chromate industry, in the manufacture of chrome pigments and in the use of zinc and lead chromates. Hueper (1942) thought that the true carcinogen was produced by the action of chromium on some endogenous material. A recent case of bronchogenic carcinoma in an Elektron[1] polisher, described by Asang (1952), showed long retention of insoluble Cr compounds in the lungs (8–10 mg. Cr) even seven years after leaving the work. On the other hand, Miller (1956) states that only those exposed to the mists of water-soluble chromates (Cr^6) develop lung tumours, but, of course, these must undergo reduction to be retained.

In Britain, however, Bidstrup (1951) could find only one case of lung cancer (later fatal) in a radiographic survey of 724 workers in three chromate factories. In a later study of the 723 workers in the six years following the first survey, Bidstrup & Case (1955) found that, of 59 deaths, 12 had been certified as due to cancer of the lung, 9 to tumours of other sites and 38 as due to other causes; in addition 1 other lung-cancer death and 2 living patients with lung cancer were known but not included. Only the lung-cancer cases were found to be significant, being almost four times that expected, all statistically important factors having been allowed for. It is likely that the hazard will appear much higher than this with the passage of years as more and more workers die.

[1] Elektron metal is an alloy of Mg with small amounts of Al, Zn, Si and Mn. The metal objects are dipped in alkaline dichromate to produce a coating of Al chromate and Mg chromate.

As in all occupational cancers the latent or induction period is long, in this series 21 ± 10 years; and the tumours may appear many years after exposure in the industry has ceased.

Nothing is known as to the active agent but it appears to the writer that it is likely to be a trivalent chromium compound (Goldblatt & Goldblatt, 1956).

3. Nickel

In a paper enumerating certain substances which cause cancer in industry, Bonser *et al.* (1955) suggest that nickel may induce cancer of the respiratory tract, but add that the proof that the tumours are industrial in origin is doubtful, and that no experimental proof has been adduced. This is a surprising statement inasmuch as carcinoma of the mucous membranes of the nose and air sinuses, and bronchial carcinoma, are prescribed diseases for the purposes of the National Insurance (Industrial Injuries) Act, 1946, and the nature of the occupation is given as decomposition of a gaseous nickel compound. Manifestly the framers of the prescription had $Ni(CO)_4$ in the Mond process in mind (see Amor, 1939), and left no doubt that they believed the condition to be industrial even if they did not indict nickel metal or even the carbonyl as such. The indictment was of an industrial process and it may be that Bonser and her co-workers imply that nickel, as such, is doubtful as the industrial cause. The problem is presented by Goldblatt & Goldblatt (1956), and the two common theories —the "arsenic theory" and the "metal theory"—are discussed.

The "arsenic theory" (metallic arsenides) is out of favour because: (i) there is no collateral evidence of arsenical affections (dermatitis, skin cancer); (ii) other dusty industries in which sulphuric acid with a high As_2O_3 content has been used for many years are not prone to cases of ethmoid or lung cancer; (iii) heavy exposure to arsenical dusts sufficient to perforate the nasal septum does not induce such cases. Nevertheless Perry (1947) found a raised As content in the lungs, hair and urine of two nickel workers in whom extirpation of the lung had been successfully performed.

The "metal theory" rests perhaps on stronger grounds and, inasmuch as cases of $Ni(CO)_4$ poisoning still occur, we cannot ignore the likelihood of deposition of nickel at susceptible points. Indeed, Hunter (1955) does not discard either nickel or the carbonyl as possible causes. For an account of the removal of nickel after exposure to $Ni(CO)_4$, see Barnes & Denz (1951).

Nickel is not an inert substance; dermatitis occurs frequently following exposure to nickel. Calnan & Wells (1956) patch-tested hundreds of patients and found nickel to be the commonest specific skin sensitizer, nearly always in women (ear-rings, suspenders, spectacles, brassière fastenings, bracelets, etc.). Once established, the sensitivity was usually maintained, and secondary spread was a feature.

Schinz & Uehlinger (1941) and Hueper (1951, 1952) induced tumours in highly artificial conditions, and Løken (1950) found three cases (two more later) of bronchogenic carcinoma in men working on electrolytic refining of nickel (no carbonyl involved) in a single factory; one lung, analysed eight years after cessation of exposure, contained 1 mg./g. nickel. It is, perhaps, significant that the nickel mineral used in most countries consists of a mixture of NiFeS, $CuFeS_2$ and Fe_9S_8, with small amounts of Au, Ag, and Pt.

Cancer of the nose and ethmoid is a rare condition in the

machine-shop in Canada, and Gilman & Vesselinovitch (1955) confirmed this experimentally (cf. Blanding, King, Priestley & Rehner, 1951) on mouse skin with the soluble oil formulations which produced so much higher a response than that obtained by Woodhouse (1951, 1952) with mineral oil fractions that they cast suspicion on the additives in the formulations. Cruickshank & Squire (1950) found that rabbit skin was more responsive than mouse skin; and also Hieger & Woodhouse (1952), in very careful experiments, showed conclusively that rabbit skin is much more responsive to certain oil fractions and stated that ". . . it is unsatisfactory to exclude carcinogenicity on the basis of tests on mice only". Berenblum & Schoental (1947) had come to similar conclusions with certain constituents of coal-tar. But Woodhouse (1951, 1952) found 9:10-dimethyl-1:2-benzanthracene more potent on mice than on rabbits. The great need is for quantitative analysis of mineral oils, but this, as stated by Hieger and Woodhouse, is an immensely difficult matter.

8. Aromatic Amines

Goldblatt (1947, 1949) reviewed the problem of cases of occupational cancer of the bladder induced by aromatic amines and analysed 100 cases collected in two factories in the period 1934–47. Case and his co-workers (Case, 1953; Case, Hosker, McDonald & Pearson, 1954) made a statistical analysis of all death-certificates in England and Wales for 1921–50, in which tumour of the bladder was mentioned. From the data thus obtained the following results emerged:

Nominal roll of workers engaged in (i) manufacture, (ii) use or (iii) purification of one or more of aniline, 1-naphthylamine, 2-naphthylamine and benzidine . .	4,622
Expected number of death-certificates (cause: cancer of the bladder) in the three groups allowing for age and date of entry into the industry	3–5
Number of cases of bladder tumour in the three groups	at least 341
Number of these 341 cases which had contact with one or more of 1-naphthylamine, 2-naphthylamine and benzidine . .	298
Including aniline (4) and magenta (9) .	311
Number of these 311 who appeared in nominal roll, i.e., worked in the industry for more than six months . . .	262
Number of death-certificates (cause: cancer of the bladder) among the 262 . .	127

Thus, the over-all risk of dying from bladder cancer in the manufacture of synthetic dyestuffs was about 30 times that in the general population. It was also concluded that there was a definite hazard of bladder cancer in the manufacture of auramine (a diphenylmethane dyestuff) and of magenta (a triphenylmethane dyestuff). It may be recalled that the earliest cases of occupational bladder cancer described by Rehn (1895) were among workers in magenta manufacture. Case & Pearson (1954) found no evidence to suggest that the use or manufacture of aniline during 1910–52 has been a cause of bladder cancer.

From Case's analysis the number of fatal tumours already found among the manufacturing workers was 243 out of 2,466 during 1915–50, and the calculated forecast is that a further 243 fatal tumours will be found, even if no further exposure takes place.

Scott & Williams (1957) have presented a valuable guide to practice in industries making or using bladder carcinogens. The substitution of Tobias acid (by amination of sulphonated 2-naphthol) for the old method of first aminating the naphthol and then sulphonating the 2-naphthylamine, obviates the need for separation of the free amine, thus eliminating the cancer hazard, provided that conditions are such as to minimize the instability of the acid as well as the incomplete sulphonation of the naphthol.

Benzidine, an undoubted carcinogen in men and animals, is closely related to the important intermediates *o*-tolidine, dianisidine and dichlorobenzidine, but these compounds are not carcinogenic. 1-Naphthylamine, however made, contains 2-naphthylamine which probably constitutes its hazard. The *N*-alkyl and *N*-aryl derivatives of the naphthylamines are not carcinogenic. Sulphonation of the bases eliminates carcinogenicity. The making of naphthionic acid and its salts (1-naphthylamine-4-sulphonic acid) entails hazard because the amine is the starting material; the sulphonation is not complete, thus leaving free 1-naphthylamine and 2-naphthylamine in the wash-waters and in the tar residues.

Case & Hosker (1954) traced statistically that during 1936–1950 there appeared a marked increase in a large centre of the rubber industry and associated it with the use in that period of a condensation product of the naphthylamines with metaldehyde, which, however, contained 2–5% of unreacted bases. The material was at once withdrawn from manufacture and use; but the potential of bladder tumours in exposed workers will require many years to discharge.

Walpole, Williams & Roberts (1952, 1954) having shown that 4-aminodiphenyl was a potent bladder carcinogen in dogs, there followed the report of Melick, Escue, Naryka, Mezera & Wheeler (1955) that in an American factory where this compound was manufactured from 1935 till 1955, 11.1% of 171 workers developed bladder tumours, the induction time varying from 5 to 19 years and the exposure times from 1¼ to 19 years. The rubber antioxidant made from this compound by condensation with an aliphatic ketone does not appear to be a bladder carcinogen when fed for long periods to dogs (personal communication from Dr E. R. Wheeler).

For the control of amino compounds in the clothing and urine of workers, analytical methods have been given by Burt & Strafford (1956) and Glassman & Meigs (1951). For the early diagnosis of bladder tumours Crabbe (1952) and Crabbe, Cresdee, Scott & Williams (1956) have described the application, in the field, of the Papanicolaou technique and the results of the examination of 1,800 workers. O 63 men examined both by the cytological technique and by cystoscopy, the cytological procedure failed to anticipate the later cystoscopic findings in only 6; but of 28 men later found to be cystoscopically negative, 10 were reported positive by cytology. The detection of abnormal cells in the urine is greatly facilitated by the concentration method of Rofe (1955, 1957).

Bonser, Clayson & Jull (1951)[*], using the method of Clayson (1950) for estimating 2-amino-1-naphthol conjugates, showed that the susceptibility of various species to the carcinogenic action of naphthylamine (*per os*) was directly

[*] See also Bonser, Clayson & Jull, p. 146 of this number of the Bulletin. —Ed.

general population. The mean induction time of the occupational tumour is about 23 years. We suggest that the carcinogen enters the ethmoid sinus and that the rapid decomposition of the carbonyl in the tissues leads to the deposition of very finely divided nickel in the thin mucous membrane, which is very closely applied to the bone. Retention would be accentuated by any degree of stenosis at the fine orifices connecting the sinuses to the nasal meatus, say from slight oedema. It is significant that Løken makes no mention of nasal or ethmoid tumours in his five cases, a carbonyl process not being involved. Barnes & Denz (1951) showed that rats exposed to $Ni(CO)_4$ frequently develop severe and extensive fibrosis of the lungs, a reaction evidently due to a stable deposition of nickel or a nickel-protein complex in the alveolar walls. The significance of the mild cases of $Ni(CO)_4$ intoxication in factories may become apparent in later years.

4. Haematite

Faulds & Stewart (1956) have found that, in the six-year period 1948–53, 15% of 89 consecutive necropsies of haematite miners showed cancer of the lung, and that the tumours usually lay in the areas of fibrosis caused by sidero-silicosis; they consider that the latter condition predisposes to carcinoma of the lung. The view of Bonser *et al.* (1955), that a modification of the action of SiO_2 by asbestos and by iron oxide may turn it into a carcinogen, recalls that Kennaway & Kennaway (1947) found no evidence of an increased cancer-rate among workers exposed to the risk of silicosis except in the case of metal-grinders. Turner & Martin (1949) confirmed this by finding that 60% of deaths from cancer in grinders with silicosis are due to cancer of the lung. It may also be recalled that Kettle (1932) found that a thin layer of iron oxide over quartz particles prevents the development of silicosis in animals. But Doll (1953) attributes any increased cancer hazard in grinders to "some other, and more specific, industrial hazard" and not to silica.

5. Coal and Graphite

Kennaway & Kennaway (1953) found a lower incidence of lung cancer in coal-miners than in the general population, thus going further than Gooding (1946) who found no evidence of increased primary lung cancer in pneumoconiotic anthracite-miners. Moreover, it appeared that there was an almost inverse relation between the two conditions. James (1955) casts more light on some selected findings of Stocks (1952) that the relative incidences of lung cancer in the period 1946–49 in the South Wales towns of Merthyr Tydfil (high coal-miner population), Cardiff and Swansea (few coal-miners) were as 77 : 126 : 132, the lower incidence being maintained in the mining area even after correction for the larger population and urbanization of the latter two towns. For 1947–52 James found primary lung cancer at necropsy in 3.3% of 1,827 South Wales coal-miners and in 5.4% of 1,531 non-miners over the age of 21. In both series the frequencies of cell types and of metastases were of the same order. Where massive fibrosis and cancer were present in the same lungs, it was relatively unusual to find the two conditions near each other, which may suggest an antagonism between the cancerizing process and the tubercular process of progressive massive fibrosis (cf. the same thing in silicosis).

Graphite pneumoconiosis according to Parmeggianni (1950) is a relatively mild condition in spite of the 11% SiO_2 in Italian graphite (56% C, 11% SiO_2, 8.6% Al_2O_3, 3% Fe_2O_3), but the modified action of the silica does not appear to entail an increase in cancer.

6. Gas and Coke

Kennaway & Kennaway (1947) found that the certified deaths from cancer in gas-workers during 1921–38 exceeded the expected by 29–184%. Doll (1952) examined the mortality data of 840 pensioners over 60 years of age from a single large London gas-company, who died in the period 1939–48. The expected deaths from lung cancer were 10.4 calculated from data for England and Wales, and 13.8 from estimated London data, whereas 25 were found (*P* less than 0.001 and 0.01 respectively). This is very significant. Sixteen of the 25 men had probably worked in contact with tar, 23 having been employed in the gas-works for 30 years or more. Doll found only 4 fatal cases of skin cancer as against 2.4 expected from rates for England and Wales; these seem few when we note that Fisher (1953), at a tar distillery in South London, found that 60–100% of his men exposed to tar for 30 years or more showed varying degrees of skin changes.

The great improvement in working conditions may now have removed the twofold hazard of lung cancer found by Doll (1952) in pensioned gas-workers. In the National Coal Board's coking-plants Reid & Buck (1956) could find no evidence among men dying between 1949 and 1954 to indicate an increased hazard of lung cancer to all categories of workers. This may be related to the newer retort designs and the less emphasis on cracking and illuminant production in both coal-gas and coke processes.

7. Pitch, Tar, Soot and Mineral Oil

In some sense the problem of industrial skin cancers has been resolved, inasmuch as the clinical incidence, signs, symptoms, treatment and prognosis are understood and experimentally one or more carcinogens have been isolated from soot, pitch and tar. The active agents in mineral oil have not been identified. Fatal cases still occur. In 1955, 211 cases (18 fatal) were notified to the Chief Inspector of Factories: 48 due to mineral oils and 163 to pitch and tar. A classical fatal case of chimney-sweep's scrotal cancer on the left side (see Henry, 1946)[2] was reported in the same year. Goulden & Tipler (1949) obtained from domestic soot the fluorescence equivalent of 290 mg./kg. of 3:4-benzopyrene. The cutting-oil formulations used in machine-shops vary according to the speed of the tools. For low speeds mineral, vegetable or animal oil (with addition of phosphorus, sulphur or chlorine compounds) suffices; but, for high speeds, oil–water emulsions containing surface-active agents, rust inhibitors and disinfectants are used. Much oil is thrown off the machine and contaminates the workers. Cruickshank & Squire (1950) found that about one-third of 138 workers in three factories had hyperkeratoses or warts, increasing with length of service. Cruickshank & Gourevitch (1952) found, of 37 cancers of the hand and forearm (1941–50) and 34 cancers of the scrotum (1940–48) recorded in Birmingham, 30 derived from 88,859 meta-workers and 41 from the whole) remaining population of solme 271,000. Mastromatteo (1955 found six cases of squamous carcinoma and one of wart in a

[2] See also Henry, *Brit. med. Bull.* 1947, 4, 389.—Ed.

related to the fraction of the dose thus eliminated and in the following order: rabbit:rat:mouse:dog as 1:2:4:5. Moreover, in the dog the urine-plasma concentration was about 200. This difference is evidently a real characteristic, for Henson, Somerville, Farquharson & Goldblatt (1954); Somerville, Henson, Cooke, Farquharson & Goldblatt (1956) and Somerville, Henson, Cooke and Goldblatt have injected 2-[8-^{14}C]naphthylamine intraperitoneally in dog, rabbit, guinea-pig, mouse and rat and found 87%, 86%, 84%, 80% and 65% respectively of the dose excreted in the urine but at different rates (paper in preparation).

Bonser, Clayson, Jull & Pyrah (1956) showed that all their dogs that had been fed 2-naphthylamine (purified or very highly purified[4] by Case's method of gradient sublimation) for two years or more (max. cumulative dose, 310 g.) developed bladder tumours. Arachis oil solution of 2-naphthylamine allowed to stand for four weeks and injected subcutaneously induced local sarcomata and hepatomata; freshly prepared solutions were much less effective in this respect. Using Jull's technique (1951) for implantation of paraffin pellets containing the base into the bladder of mice, Bonser, Bradshaw, Clayson & Jull (1956) induced carcinoma, benign tumours and squamous metaplasia, but to a much less extent than with the metabolite 2-amino-1-naphthol. Similar results were obtained with 4-aminodiphenyl. The authors conclude that both these bases possess slight carcinogenic activity; but see also Bonser, Crabbe, Jull & Pyrah (1954). With 1-amino-2-naphthol, a very high yield of tumours was obtained; similarly with 3-hydroxy-4-aminodiphenyl and its 4'-nitro derivative. These findings strongly sustain the *ortho*-hydroxyamine theory. However, some nitrogenous compounds injected directly into the bladder may act as carcinogens, as was shown by Bonser, Clayson & Jull (1954) with 3 : 4-5 : 6-dibenzocarbazole (0.25% weekly for 12 months—transitional cell papillomatosis 2½ years later), and was first observed by skin-painting by Boyland & Brues (1937) and Boyland & Mawson (1938); sarcomata were produced by subcutaneous injection, and sarcomata and cholangiomata by intraperitoneal injection.

[4] Impurities commonly found in 2-naphthylamine include 1-naphthylamine, pyrene, 3 : 4-5 : 6-dibenzocarbazole, 2 : 2-dinaphthylamine, 1 : 2-5 : 6-dibenzophenazine (Case & Pearson, 1952).

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AROMATIC AMINES AS CARCINOGENS IN INDUSTRY

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1. Dyestuffs Industry

The history of cancer as an occupational disease is closely linked with that of the manufacture of synthetic dyestuffs from coal-tar. This industry dates from Perkin's exploitation of his discovery of mauve, accidentally made, in 1856, when he was trying to synthesize quinine (Perkin, 1856). The manufacture of triphenylmethane dyes, which rapidly developed from this beginning, required for the first time the production on a large scale of aromatic amines—aniline and the toluidines and xylidines—from coal-tar. For a long time these amines were used for the manufacture of dyes as crude mixtures of variable composition, characterized only by the ranges of temperature over which they distilled. Their acute toxic effects on man were quickly appreciated as a result of unfortunate experiences, but chronic toxic effects were not expected.

Nearly 40 years later, however, Rehn (1895) drew attention to the fact that four men whom he was treating for tumours of the urinary bladder all worked in the same dyestuffs factory, and further inquiry revealed that they were all employed in making the same dye, fuchsin (magenta). Rehn's suggestion that the tumours in these men were due to their environment was received with scepticism which increased as a further 60 years passed and no further tumours were attributed to the manufacture of this dyestuff in any country. But in 1954 Case & Pearson published statistical evidence showing that there had been a significant excess of bladder tumours in Great Britain, during the previous 35 years, amongst men who made magenta. The facts established by these observations, 60 years apart, have not yet been adequately explained, despite an abundance of theories. The suspicion has been entertained at one time or another that aniline can cause cancer of the bladder, which for many years was known in the industry as " aniline cancer ", and Hergt (personal communication) believed that some of the early cases in Germany could be attributed to toluidines; but there is no satisfactory evidence that any of the simpler aromatic amines already mentioned are, in fact, carcinogenic. Walpole, Williams & Roberts (1952) suggested that the early tumours in the German industry were due to contamination of these amines by naphthylamines and xenylamines, but such an explanation is scarcely applicable to tumours occurring in British workmen as late as 1920–53. It has also been suggested that Rehn's cases were exposed to other aromatic amines such as 2-naphthylamine and benzidine, which are now known to be bladder carcinogens in man, but in the British factories in question these amines were not made or used. The possibility that magenta itself, a triphenylmethane dyestuff, is carcinogenic, has not been neglected. Yoshida, Schimauchi & Kin (1941) claim to have obtained papilloma of the bladder in rats following intravesical implantation of the dyestuff in collodion, but Willheim & Ivy (1953) saw no tumours of any kind in rats to which it was given in the diet in high concentration, and in the experiments of Bonser, Clayson & Jull (1956) no significant yield of tumours resulted in mice from repeated oral dosing.

The sulphonated triphenylmethane dye, Light Green SF Yellowish (Schiller, 1937; Harris, 1947), produces sarcoma at the site of its repeated subcutaneous injection in aqueous solution in rats. No distant tumours are produced, however, and when given by mouth the dye appears inactive (Allmark, 1956). There is no evidence whatever that its manufacture is associated with any hazard to the workers involved.

Two cases of bladder tumour were attributed by Müller in 1933 to the manufacture of the dyestuff auramine, a derivative

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of diphenylmethane. This manufacture was incriminated on statistical grounds by Case & Pearson in 1954. They described eight more cases, in Great Britain, attributable to this cause. Bonser *et al.* (1956) produced a few hepatomata in mice with a commercial sample of the dyestuff given in the diet, but all the chemicals involved in its manufacture have not been fully investigated and a conclusive explanation for the bladder tumours in workmen making this dyestuff has not yet been reached.

The discovery by Griess of diazotization in 1858 and of the coupling of diazonium salts in 1864 led to the development of a new class of coal-tar dyestuffs, the azo dyes, for which new aromatic bases, including the naphthylamines and benzidine, were required as intermediates. Occupational cancer of the bladder was first attributed to naphthylamine at the turn of the century (Leichtenstern, 1898). 2-Naphthylamine was accepted as a cause, on epidemiological evidence, shortly after the First World War (International Labour Office, 1921) and 16 years before bladder tumours were induced with it in dogs (Hueper & Wolfe, 1937; Hueper, Wiley & Wolfe, 1938). Although no experimental evidence is available to incriminate 1-naphthylamine, Case, Hosker, McDonald & Pearson (1954) presented evidence of a significant excess of bladder tumours amongst both users and makers of the commercial product, which contains 4% of 2-naphthylamine, 23 years after cases were first attributed to it by Wignall (1929).

Benzidine, which has been under suspicion since the 1920's, was not accepted as a cause by the Americans Gehrmann, Bulger & Fleming as late as 1949, despite the attribution to it of numerous cases by workers in different countries. For many years, Maguigan in the USA maintained that benzidine was a cause of bladder cancer in industrial workers, and in 1950 Spitz, Maguigan & Dobriner demonstrated its carcinogenicity in rats and dogs. Case *et al.* (1954), in their survey of the British chemical industry already referred to, obtained statistical evidence that a high incidence of bladder tumours had developed in men exposed to benzidine, and so replaced suspicion by statistical proof.

Suspicion that azo dyes themselves might be carcinogenic was aroused by early work by Fischer (1906) on scarlet red. Intensive study of the subject was initiated by Japanese workers in the early 1930's and taken up later by others, including Orr, Kirby and Peacock in Great Britain, and Shear and more recently the Millers in the USA. *o*-Aminoazotoluene was found to be a potent liver carcinogen in rats and mice, and to produce bladder tumours in rats. 4-Dimethylaminoazobenzene (butter yellow) was found to be even more active in inducing liver tumours. Numerous related azo compounds have since been examined and many of these produce neoplasms, particularly of the liver, in rats and mice. Work in this connexion has often been reviewed (Miller & Miller, 1953, 1955; see also Miller, Miller & Finger, 1957), and will not be discussed further here. Bladder tumours have been produced in dogs with *o*-aminoazotoluene and butter yellow (Nelson & Woodard, 1953) but there is as yet no published evidence that any azo compound has caused cancer in man.

2. Other Industries

Wilson, De Eds & Cox in 1941 made a toxicological study of 2-acetamidofluorene, which was of interest on account of its insecticidal properties. They found that on continued oral administration to rats it produced tumours of several organs, notably the bladder, liver and lungs. As a result the compound has never been manufactured on a scale sufficient for its carcinogenic action to become an industrial hazard. Its versatility as a carcinogen was confirmed by later work, reviewed by Bielschowsky in 1947. More recently Morris & Eyestone (1953) have obtained bladder tumours with it in dogs. Its action and that of numerous related substances have been widely studied, especially during recent years by the Millers and their associates in Madison, Wisconsin, and by Morris and his co-workers in Bethesda, Maryland (Miller, Sandin, Miller & Rusch, 1955; Miller & Miller, 1955; Morris, 1955).

Interest in 4-aminodiphenyl (xenylamine) as a potential carcinogen was first stimulated by learning from the literature that it had been isolated by Hofmann in 1862 from the crude mixture of bases derived from coal-tar which was an intermediate stage in the manufacture of triphenylmethane dyes (Walpole *et al.* 1952), and also by the demonstration of carcinogenic activity in the related substances *NN*-dimethyl-4-aminodiphenyl (Miller, Miller, Sandin & Brown, 1949) and benzidine (Spitz *et al.* 1950). As 4-aminodiphenyl produced a variety of tumours in rats (1952) and bladder tumours in dogs (1954), Walpole, Williams & Roberts forecast that bladder tumours would develop in men exposed to it. Melick, Escue, Naryka, Mezera & Wheeler (1955) found bladder tumours in 19 men engaged in its manufacture in the USA since 1938. Thus it had taken 17 years for this amine to manifest its carcinogenic potential and during that time 171 men had been exposed to risk. It will be many years before the full extent of the damage caused by this manufacture, now abandoned, will be known. In Great Britain manufacture of 4-aminodiphenyl was never started, because of the experimental evidence quoted.

One of the uses of 4-aminodiphenyl in the USA was in the manufacture of an antioxidant for rubber (Case, 1954). A similar condensate, prepared from naphthylamine and an aldehyde, was marketed in Great Britain as a rubber antioxidant as early as 1927. Its manufacture was abandoned in 1949 when the danger from free naphthylamines in the final product became apparent. Case & Hosker (1954) demonstrated an excess of cases of bladder tumours in rubber workers in a county borough where this naphthylamine aldehyde condensate had been used for many years. The fate of American rubber workers exposed from 1938 to 1955 to the xenylamine condensate is no doubt being followed with concern.

While considering rubber workers it is well to remember that the use of benzidine as a hardening agent is still advocated in text-books of rubber technology. Such a use must be regarded as hazardous. Both benzidine and 1-naphthylamine have also been extensively used in textile printing. Although no tumours have been attributed to their use in this industry it would seem advisable to handle them there with precautions similar to those in the chemical industry.[1] Benzidine has been used for many years in the manufacture of " security paper " to produce a stain in the presence of bleach and thus to expose attempts to delete and alter writing (Simons, 1951). It is expected that this use of the compound will produce its quota of tumours. The suggested use for this purpose of other carcinogens, including naphthylamines and aminodiphenyls (Simons, 1937) and 4 : 4′-diaminostilbene (Smith, 1937),

[1] See also Goldblatt, p. 136 of this number of the Bulletin.—Ed.

which produces a high incidence of liver tumours in rats (Walpole & Williams, unpublished), must also be regarded as hazardous.

The human exposure involved in using benzidine in clinical and forensic laboratories as a test agent for occult blood is probably insignificant, but its use for spraying chromatograms in biochemical laboratories must be regarded as potentially hazardous.

Many other carcinogenic aromatic amines already exist, and it is inevitable that technologists will look for new amines to produce improved products and unique technical effects.

3. Examination of New Aromatic Amines

With the object of learning more about the effects of ring substitution on the carcinogenic properties of amines known to be active in this respect, we have examined a number of substituted aminodiphenyls, diaminodiphenyls, aminostilbenes and diaminostilbenes. The results will be published in detail elsewhere, and we give only a summary of the more significant of the findings.

a. Aminodiphenyl Derivatives

Table I relates to derivatives of the 4-aminodiphenyl series. In the first instance these compounds were given by repeated subcutaneous injection in arachis oil, at doses near the maximum tolerated, to groups of 24 male albino Wistar rats. For each are shown in Table I the total dose in g./kg. and the main sites of tumour incidence in descending order of frequency. Sarcomata at the injection site, which developed late in the experiments with several of these substances, are probably to be attributed to the oily vehicle and are not included.

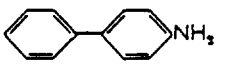
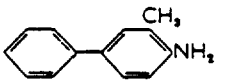
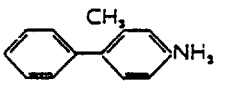
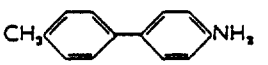
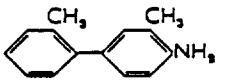
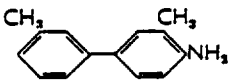
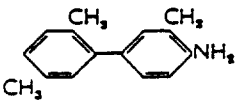
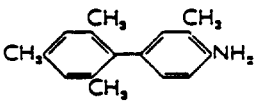
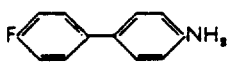
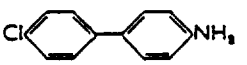
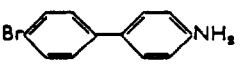
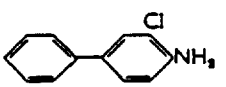
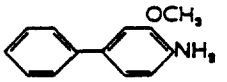
Consideration of the detailed results of these experiments in rats leads to the conclusion that the introduction of a methyl group into the 3-position in 4-aminodiphenyl, with or without methyl groups in other positions, enhances carcinogenic efficacy, especially for the intestine. Methyl substitution in the 2-position, on the other hand, results in a compound which produces liver tumours only, and these in relatively low yield, while 4′-methyl-4-aminodiphenyl, in very large doses, causes tumours of the acoustic sebaceous gland, intestine and liver in descending order of frequency.

The results obtained with 4′-fluoro-4-aminodiphenyl, which produces tumours of the liver and kidney in high yield (Hendry, Matthews, Walpole & Williams, 1955)[1], and with its chloro- and bromo-analogues, are in line with the observations of other workers who have fed to rats derivatives of 2-acetamidofluorene halogenated in the 7-position. Thus 7-fluoro-2-acetamidofluorene is more active as a carcinogen than acetamidofluorene itself (Miller *et al.* 1955), while the corresponding chloro-compound is less active and the iodo-derivative appears inactive at any site (Morris, 1955). Even in the butter-yellow series of liver carcinogens, substitution of fluorine, chlorine and bromine in the 4′-position has similar over-all effects upon carcinogenic potency (Miller, Miller & Finger, 1953; Miller, Sapp & Miller, 1949; Kuhn & Quadbeck, 1949).

The activity of 3-methoxy-4-aminodiphenyl in producing bladder tumours recalls a similar result obtained by Hackmann (1956) on feeding 2-amino-3-methoxydiphenylene oxide to rats.

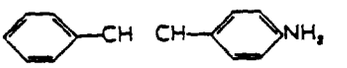
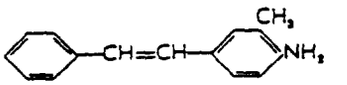
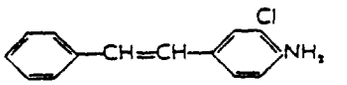
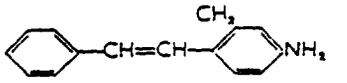
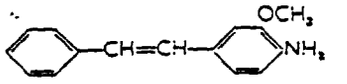
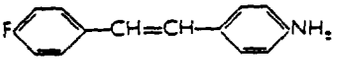
[1] See also Matthews & Walpole (1958) *Brit. J. Cancer*, 12 (In press)

TABLE I. TUMOURS PRODUCED IN RATS BY THE REPEATED SUBCUTANEOUS INJECTION OF 4-AMINODIPHENYL AND SOME DERIVATIVES THEREOF

Compound	Total dose (g./kg.)	Organs in which tumours arose in significant yield
	5.0	Intestines, liver
	1.2	Intestines, acoustic sebaceous gland
	2.4	Liver
	10.1	Acoustic sebaceous gland, intestine, liver
	2.8	Intestines, acoustic sebaceous gland
	2.4	Intestines, acoustic sebaceous gland
	1.4	Intestines, liver
	1.4	Intestines, liver
	2.0	Kidney, liver, intestines
	3.3	No significant yield at 700 days
	4.1	No significant yield at 800 days
	7.0	Intestines
	4.4	Bladder

The derivatives of 2-aminodiphenylene oxide (aminodibenzofuran), and those of 2-aminofluorene, constitute two series of compounds which may be regarded as derived from the corresponding substitution products of 4-aminodiphenyl by the

ABLE II. TUMOURS PRODUCED IN RATS BY THE REPEATED SUBCUTANEOUS INJECTION OF 4-AMINOSTILBENE AND SOME DERIVATIVES THEREOF

Compound	Total dose (g./kg.)	Organs in which tumours arose in significant yield
	0.2	Acoustic sebaceous gland (variable yield of local sarcomata)
	0.2	Local sarcomata only (less than 190 days)
	0.2	Local sarcomata only (less than 200 days)
	0.24	Local sarcomata only (less than 250 days)
	0.25	Local sarcomata only (302–625 days)
	0.2	Acoustic sebaceous gland, liver, intestines

insertion of an —O— or —CH_2— bridge in the 2:2′-position. Carcinogenic activity in these series, and in others with different bridging atoms or groups, has been investigated and kept under review, on a comparative basis, by the Millers and their associates (see their publications from 1955 onwards).

b. Aminostilbene Derivatives

In view of their possible future use in industry, we have carried out similar tests with analogous substitution products in the 4-aminostilbene series. Haddow, Harris, Kon & Roe (1948) obtained local sarcomata at the site of subcutaneous injection, carcinomata of the " acoustic duct " and mammary adenomata in rats with 4-aminostilbene, 4-*NN*-dimethylaminostilbene, 4-*NN*-dimethylamino-2′-methylstilbene and 1-(4′-*NN*-dimethylaminophenyl)-2-(1′-naphthyl)-ethylene. In our experiments 4-aminostilbene and its substitution products were given to male rats by repeated subcutaneous injection in arachis oil (daily or twice weekly) up to a total in all cases of about 0.2 g./kg. The results shown in Table II may be summarized as follows. 4-Aminostilbene itself produced a high yield of carcinomata of the acoustic sebaceous gland (after 175–642 days), with local sarcomata in a yield which appears to depend in some way on the precise schedule of dosing. With 3-methyl-, 3-chloro- and 2-methyl-4-aminostilbene, local sarcomata only were observed. These tumours appeared in almost every animal treated and all arose between 150 and 250 days after injection. These tumours must be attributed to the specific action of the respective compound and not to the oily vehicle used for its injection. In one feeding experiment with 3-methyl-4-aminostilbene (average total dose 0.35 g./kg.), two of four animals surviving for 190 days or more developed tumours of the acoustic sebaceous gland. The injection of 3-methoxy-4-aminostilbene produced local sarcomata in 18 of 24 animals, but these tumours appeared much later (302–625 days). 4-Amino-4′-fluorostilbene gave the same high yield of tumours of the acoustic sebaceous gland as 4-aminostilbene itself and produced tumours of the liver and intestine in significant yield but no local sarcomata.

Fewer compounds in the 4 : 4′-diaminostilbene series were tested. We have shown that the parent diamine, in a total dose of 0.2 g./kg., produces tumours of the liver, with some late local sarcomata. On the other hand 4:4′-diamino-3:3′-dichlorostilbene, in comparable dose, produced only local sarcomata. These occurred in all but one of 24 animals in 200–400 days. 4:4′-Diamino-2:2′-dichlorostilbene was less toxic and, given in a total dose of 1.4 g./kg., yielded liver tumours in 18 of 24 animals, a few tumours of the intestine and local sarcomata.

The interpretation of these results, and in particular the explanation of the differences in the site of action of these related chemicals, must await further experiment. In the meantime they show that carcinogenic activity in some form is a property common to many derivatives of 4-aminodiphenyl and 4′ : 4′-diaminodiphenyl and of 4-aminostilbene and 4 : 4′-diaminostilbene.

4. Conclusions

The history of occupational cancer of the bladder shows that many years may elapse before the danger from an industrial carcinogen is recognized or even suspected. Sixty years of scepticism passed before Rehn's original indictment of fuchsin manufacture in Germany was confirmed in Great Britain; 23 years elapsed between the attribution of the first case to naphthylamine and the general recognition of the hazard from 2-naphthylamine; for over 30 years benzidine was under suspicion before it was universally accepted as a bladder carcinogen in man; 25 years passed before bladder tumours were discovered in rubber workers exposed to naphthylamine-aldehyde condensates in Great Britain and, as a more recent example, 4-aminodiphenyl had been manufactured in the USA for over 17 years before the danger involved was pointed out.

Every year that inadequate precautionary measures are taken, the final yield of bladder tumours increases. The chemical industry has taken active measures to combat this danger. The manufacture of 2-naphthylamine has been abandoned in Germany, Switzerland and Great Britain, and rubber antioxidants from 1- and 2-naphthylamine are no longer made in Britain. The publication by the Association of British Chemical Manufacturers of a code of practice for the handling of known bladder carcinogens (Scott & Williams, 1957) has laid down a standard to be aimed at in achieving safe working conditions. If all these measures are successful, the future yield of tumours due to known carcinogens in the dyestuffs industry should fall rapidly in the next 20 years, but the casual use of these dangerous substances in other industries must be a matter for concern.

We present the summarized results of our tests of amines and diamines as a guide to chemists and technologists who may contemplate using them in the future. In this way we

hope to anticipate some of the dangers from compounds of this nature and thus prevent a recurrence of the unfortunate experiences of the past.

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Notes on Contributors

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DR F. BIELSCHOWSKY was Privatdozent at the University of Freiburg and lecturer on metabolic diseases in Madrid before coming to Britain. He worked from 1939 until 1948 in the Department of Pathology of the University of Sheffield. After collaborating with Professor H. N. Green in an investigation of the mode of action of sulphanilamide, he began in 1942 to work on problems of cancer, studying the action and the metabolism of aromatic amines. His earlier work dealt with problems of the metabolism of nucleic acids and of lipids. Dr Bielschowsky has since 1948 been Director of the Cancer Research Department of the Medical School, University of Otago, Dunedin, New Zealand, and of the New Zealand branch of the British Empire Cancer Campaign. During the last ten years he has studied the endocrinological aspects of cancer (see *Brit. J. Cancer*, 1955, 9, 80). Dr Bielschowsky has previously contributed to the Bulletin a paper on the carcinogenic action of 2-acetylaminofluorene and related compounds (*Brit. med. Bull.* 1947, 4, 382).

DR G. M. BONSER is Reader in Cancer Research in the University of Leeds and Consultant in Morbid Anatomy, St James's Hospital, Leeds. She has been engaged in cancer research for thirty years, working first on intra-thoracic cancer and later on the hormonal and genetic aspects of mammary and testicular cancer. During the last twenty-five years, she and her colleagues have undertaken a combined biological and chemical investigation of the metabolism and carcinogenic properties of aromatic amines, especially of those related to the dye intermediates. Her publications include: "A microscopical study of the evolution of mouse mammary cancer: the effect of the milk factor and a comparison with the human disease" (*J. Path. Bact.* 1945, 57, 413); with E. C. Armstrong, "The carcinogenic action of 2-acetylamino-fluorene on various strains of mice" (*J. Path. Bact.* 1947, 59, 19); and, with L. Bradshaw, D. B. Clayson & J. W. Jull, "A further study of the carcinogenic properties of ortho hydroxy-amines and related compounds by bladder implantation in the mouse" (*Brit. J. Cancer*, 1956, 10, 539). Dr Bonser contributed a paper to an earlier number of the Bulletin, on experimental cancer of the bladder (*Brit. med. Bull.* 1947, 4, 279).

PROFESSOR E. BOYLAND is Professor of Biochemistry in the University of London at the Chester Beatty Research Institute, Royal Cancer Hospital, where he has worked (except for the war years) since 1931. He has carried out work on the metabolism of aromatic compounds, the chemotherapy of cancer, the metabolism of tumours, and in the field of carcinogenesis. In work on metabolism of aromatic compounds he discovered the metabolic process of perhydroxylation (e.g., "The conversion of anthracene to 1:2-dihydroxy-1:2-dihydroanthracene" (Boyland & Levi, *Biochem. J.* 1935, 29, 2679); "The nature of the acid-labile mercapturic acid precursor excreted when animals are treated with naphthalene" (Boyland & Sims, *Biochem. J.* 1958, 68, 440)). Professor Boyland has also identified 15 metabolites of the carcinogenic 2-naphthylamine (cf. Boyland & Manson, *Biochem. J.* 1957, 67, 275). In the field of carcinogenesis he demonstrated the carcinogenic activity of dibenzcarbazoles (Boyland & Brues, *Proc. roy. Soc.* B, 1937, 122, 429), nitrogen mustards (Boyland & Horning, *Brit. J. Cancer*, 1949, 3, 118), and of the tryptophan metabolite 3-hydroxyanthranilic acid (Allen, Boyland, Dukes, Horning & Watson, *Brit. J. Cancer*, 1957, 11, 212). During the war Professor Boyland worked for the Ministry of Supply on problems of chemical warfare and for the Ministry of Agriculture on animal diseases. He received the Judd Award for Cancer Research in New York in 1948 and the medal of the Société de Chimie Biologique in 1956. Before starting cancer research he studied in the Department of Physiology of the University of Manchester, the Lister Institute for Preventive Medicine in London, and the Kaiser Wilhelm Institut für medizinische Forschung in Heidelberg. At present he is working on the causes of cancer of the bladder, intestine, lung and cervix, on the treatment of cancer of the bladder and breast, and on the metabolism of aromatic compounds, and he is interested in carcinogenic hazards, particularly in foods, contraceptives, tobacco and cosmetics. Professor Boyland contributed a paper, together with Dr F. Weigert, to an earlier number of the Bulletin, entitled "Metabolism of carcinogenic compounds" (*Brit. med. Bull.* 1947, 4, 354).

DR W. CARRUTHERS graduated as Ph.D. in chemistry at the University of Glasgow in 1949, then took up an appointment with the Medical Research Council at Glasgow to investigate the chemistry of high-boiling carcinogenic fractions of mineral oils, under the direction of Dr J. W. Cook. In 1956, he moved to Exeter, and took charge of the laboratory of the Council's new Carcinogenic Substances Research Group. The present work of the Group includes a study of the chemistry of tobacco smoke, as well as a continuation of the investigation of mineral oil fractions. A number of papers have been published incorporating the results so far obtained in the mineral oil work.

DR D. B. CLAYSON is Elizabeth and Louisa Ward Fellow in the Department of Experimental Pathology and Cancer Research in the University of Leeds. After training as an organic chemist at Oxford he came to Leeds in 1948 to work with Dr G. M. Bonser on the relation between the metabolic fate of the aromatic amines and their carcinogenic action. His published work includes: with G. M. Bonser & J. W. Jull, "An experimental inquiry into the cause of industrial bladder cancer" (*Lancet*, 1951, 2, 256); "A working hypothesis for the mode of carcinogenesis of aromatic amines" (*Brit. J. Cancer*, 1953, 7, 460); and, with G. M. Bonser, L. Bradshaw & J. W. Jull, "A further study of the carcinogenic properties of ortho hydroxy-amines and related compounds by bladder implantation in the mouse" (*Brit. J. Cancer*, 1956, 10, 539).

DR J. W. COOK is the first Vice-Chancellor of the University of Exeter and is also Honorary Director of the Medical Research Council's Carcinogenic Substances Research Group. In 1939 he was appointed Regius Professor of Chemistry in the University of Glasgow, a post which he held for 15 years. Before that he was a professor of chemistry in the University of London and research chemist to the Royal Cancer Hospital. He was responsible, with I. Hieger and C. L. Hewett, for the isolation from coal-tar pitch of a potent carcinogenic pure hydrocarbon and for demonstrating by synthetic preparation that this was the hitherto unknown 3:4-benzopyrene. He also prepared synthetically many other carcinogenic polycyclic hydrocarbons and was associated with E. C. Dodds and C. L. Hewett in the discovery of the synthetic oestrogens. Dr Cook was awarded the Davy Medal of the Royal Society in 1954 and was the Chemical Society's Pedler Lecturer in 1950. He has been President of the Royal Institute of Chemistry and was President of the Chemistry Section at the 1957 meeting of the British Association for the Advancement of Science.

DR W. M. COURT-BROWN is on the Scientific Staff of the Medical Research Council and is Director of the Group for Research into the General Effects of Radiation. He studied medicine at St Andrew's University where he graduated in 1942. After some years of work in radiotherapy, he commenced in 1950 the study of the harmful effects of ionizing radiations. He spent some time in the investigation of the acute effects, as a result of which a number of papers were published dealing with the factors governing the length of the latent period between exposure to radiation and the onset of gastro-intestinal symptoms, and he has now become mainly interested in the study of the long-term carcinogenic effects. He has published several papers on this subject, and particularly, in co-operation with Dr Richard Doll, a study of the leukaemogenic effects of radiations (*Spec. Rep. Ser. med. Res. Coun., Lond.* 1957, No. 295).

DR I. DONIACH, Senior Lecturer in Morbid Anatomy, Postgraduate Medical School of London, was formerly cancer research assistant to Dr J. C. Mottram at Mount Vernon Hospital, London. His experiments have been mostly concerned with the carcinogenic action of radioactive iodine on the rat's thyroid and with changes in thyroid function resulting from radiation. Publications include: "A comparison of the photodynamic activity of some carcinogenic with non-carcinogenic compounds" (*Brit. J. exp. Path.* 1939, 20, 227); and "The effect of radioactive iodine alone and in combination with methylthiouracil upon tumour production in the rat's thyroid gland" (*Brit. J. Cancer*, 1953, 7, 181).

DR L. A. ELSON is Reader in Biochemistry in the University of London. His first research work was on chemotherapy at Guy's Hospital Medical School, London. He was later Jenner Memorial Scholar at the Lister Institute of Preventive Medicine, London. After some years with Imperial Chemical Industries Limited in Manchester, he came to work at the Chester Beatty Research Institute, Royal Cancer Hospital, London, where he held a British Empire Cancer Campaign Fellowship and was appointed Reader in Biochemistry in 1956. Among his publications, one describes the well-known Elson and Morgan method for the determination of glucosamine and chondrosamine (*Biochem. J.* 1933, 27, 1824). He has contributed a series of papers to the *British Journal of Cancer* on the influence of the protein content of the diet on the growth-inhibitory action of carcinogenic and tumour-inhibitory compounds. At present he is mainly engaged on work on the comparative biological effects of radiation and radiomimetic tumour-inhibitory and anti-leukaemic chemicals.

DR A. GLÜCKSMANN is Senior Histologist to the Strangeways Research Laboratory, Cambridge, which he joined in 1933. He has worked mainly on

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the effects of irradiation in producing malignant diseases and the effect of irradiation in the treatment of malignant disease in man. He has developed quantitative histological methods to assess these effects, and built up probably the largest collection of biopsy and operation material obtained from irradiated human cancers. He received the Röntgen Award of the British Institute of Radiology in 1942, and was Douglas Lea Memorial Lecturer to the Hospital Physicists' Association in 1953. Among his publications are: "The influence of systemic factors on the differentiation and radiocurability of cervical cancers" (*Brit. J. Radiol.* 1956, 29, 483); "Relationships between hormonal changes in pregnancy and the development of 'mixed carcinoma' of the uterine cervix" (*Cancer, N.Y.* 1957, 10, 831); "Local factors in the histogenesis of hypertrophic scars" (*Brit. J. plast. Surg.* 1951, 4, 88). Dr Glücksmann also contributed a paper, "Quantitative histological analysis of radiation-effects in human carcinomata", to an earlier number of the Bulletin (*Brit. med. Bull.* 1946, 4, 26).

Dr M. W. Goldblatt, formerly Director of Industrial Hygiene Research Laboratories of Imperial Chemical Industries Limited, is now engaged at Pollards Wood Research Station (Institute of Cancer Research, Royal Cancer Hospital). He is a member of the Permanent International Commission on Industrial Medicine, Examiner in Industrial Health for the Diploma in Industrial Health, Member of the Editorial Committee of the *British Journal of Industrial Medicine* and Member of Executive of the British Occupational Hygiene Society. He has published papers on physiology, biochemistry, industrial toxicology and carcinogenesis, including one in an earlier number of the Bulletin entitled "Occupational cancer of the bladder" (*Brit. med. Bull.* 1947, 4, 405). Dr Goldblatt was created C.B.E. in 1955.

Professor H. N. Green is Professor of Experimental Pathology at Leeds University and Director of Cancer Research at Leeds and Sheffield Universities. He is a Sheffield graduate and, after a period as Lecturer in Pathology at Cambridge, he was for a long time Professor of Pathology at Sheffield. He has published numerous papers on many aspects of experimental pathology, including particularly the subjects of nutrition, traumatic shock and cancer. He commanded a British Traumatic Shock Team, Royal Army Medical Corps, in the Second World War. With H. B. Stoner, he wrote the book *Biological actions of the adenine nucleotides* (1950), which was largely an outcome of the shock investigations. These authors contributed previously to this Bulletin an article entitled "Effects of injury on carbohydrate metabolism and energy transformation" (*Brit. med. Bull.* 1954, 10, 38) in a symposium on "Reactions to Injury". His immunological theory of cancer (*Brit. med. J.* 1954, 2, 1374) has stimulated work in this field over a wide front.

Professor Alexander Haddow, F.R.S., graduated in medicine in 1929, at Edinburgh, where he became lecturer in bacteriology (1931–36). He joined the staff of the Research Institute of the Royal Cancer Hospital in 1936 and was appointed, in succession to Professor E. L. Kennaway, to the Chair of Experimental Pathology in the University of London and the directorship of the Chester Beatty Research Institute of the Royal Cancer Hospital in 1946. He has published a number of papers on special aspects of growth, such as the comparative pathology of tumours, viruses in relation to the aetiology of cancer, and problems of immunity affecting the transplantation of tissues. One of his main interests has been in bacterial mutation, and its importance in elucidating what he considers to be analogous problems of variation in the origin of cancer. In 1935, Professor Haddow described the growth-inhibitory property of carcinogenic compounds, and he has developed this subject and related it to the mechanism of action of tumour-producing and growth-inhibiting agents. He has been closely concerned with developments in chemotherapy. With his advice, the general plan of the Bulletin symposium published in 1947, "Chemical Carcinogenesis", was devised. He contributed to that symposium three papers, one in collaboration with G. A. R. Kon, on carcinogenesis and chemotherapy of cancer (*Brit. med. Bull.* 1947, 4, 314, 331, 417). He is at present engaged (with Professor F. Bergel, Dr W. C. J. Ross and Mr G. M. Timmis) in a study of the growth-inhibitory alkylating agents derived from nitrogen mustard.

Dr I. Hieger is a biochemist at the Chester Beatty Research Institute of the Royal Cancer Hospital, London. He was a member of the team of workers which under the inspired leadership of Sir Ernest Kennaway discovered the carcinogenic hydrocarbons and isolated 3 : 4-benzopyrene from pitch (Cook, J. W., Hieger, I., Kennaway, E. L. & Mayneord, W. V., *Proc. Roy. Soc.* B, 1932, 111, 455). He is now engaged on the investigation of carcinogenic agents of biological origin (*Proc. Roy. Soc.* B, 1957, 147, 84). Dr Hieger has published a popular book on cancer (*One in six: an outline of the cancer problem*, 1955). He has previously published in the Bulletin a paper entitled "Carcinogenic substances in human tissues" (*Brit. med. Bull.* 1947, 4, 360).

Professor E. S. Horning is Professor of Experimental Pathology (Histopathology) in the University of London at the Chester Beatty Research Institute. Previous to this, he was Reader in Experimental Pathology and, before joining the staff of the Chester Beatty Research Institute, was a scientific member of the Imperial Cancer Research Fund. Whilst holding a Rockefeller Research Fellowship, he worked at the Kaiser Wilhelm Institut, Berlin-Dahlem, and later at Washington University, St Louis, as well as at other research centres in the USA. Professor Horning was also a Beit Memorial Fellow. When at the University of Melbourne, his earlier researches were on the enzymic function of mitochondria in Protozoa. Since then he has published numerous papers in the field of cellular pathology and is now working on the relationship of hormones to carcinogenesis. Together with Dr H. Burrows, Professor Horning contributed to an earlier number of the Bulletin a paper entitled "Oestrogens and neoplasia" (*Brit. med. Bull.* 1947, 4, 367).

Dr J. W. Jull is a Saltwell Fellow of the Royal College of Physicians of London, working in the Department of Experimental Pathology and Cancer Research in the University of Leeds. He started working with Dr G. M. Bonser in 1949, and since has been interested both in the carcinogenic action of the aromatic amines and the role of ovarian and pituitary hormones in the aetiology of cancer of the breast in the human and the experimental animal. His publications include: "The induction of tumours of the bladder epithelium in mice by the direct application of a carcinogen" (*Brit. J. Cancer*, 1951, 5, 328); "The effects of oestrogens and progesterone on the chemical induction of mammary cancer in mice of the *IF* strain" (*J. Path. Bact.* 1954, 68, 547); and "Hormones as promoting agents in mammary carcinogenesis" (*Acta Un. int. Cancr.* 1956, 12, 653).

Sir Ernest Kennaway was Demonstrator of Physiology at Guy's Hospital, London, 1908–14, and was elected a Radcliffe Travelling Fellow in 1909. From 1931 to 1946 he held the post of Director of the Research Institute of the Royal Cancer Hospital, London, now the Chester Beatty Research Institute. Since 1921, he had been engaged on research on cancer, especially as regards cholesterol as a carcinogen, and cancer of the human lung and cervix. His published papers include: with N. M. Kennaway, "The relation between the incidence and incubation period of cancer in man" (*Yale J. Biol. Med.* 1944, 17, 139); "The racial and social incidence of cancer of the uterus" (*Brit. J. Cancer*, 1948, 2, 177); "The identification of a carcinogenic compound in coal-tar" (*Brit. med. J.* 1955, 2, 749). He was an Honorary Fellow of New College, Oxford, and was elected a Fellow of the Royal Society in 1934. Sir Ernest died on the 1 January 1958, while this number of the Bulletin was in preparation; a tribute to him, and further information about his life and work, are included in the Introduction to this Bulletin.

Dr A. J. Lindsey is Head of the Department of Chemistry at Sir John Cass College, London. He had a number of years in the fine chemical and scientific instrument industries before taking up his academic career in 1936. From 1940 to 1946 he served in the Royal Air Force Volunteer Reserve. His research interests are electrochemistry, radiochemistry and combustion chemistry. In this latter field, he and his research students have developed methods for the analysis of smokes and other combustion products, and they were the first to demonstrate the presence of polycyclic aromatic hydrocarbons in tobacco smoke. The ubiquity of these hydrocarbons in combustion products, and the carcinogenic nature of some of them, have made these researches of considerable interest; they have been supported by the Department of Scientific and Industrial Research and by the Medical Research Council. This work, which has been reported in about forty original papers, has been co-ordinated with similar projects in other centres, especially with that under the late Sir Ernest Kennaway at St Bartholomew's Hospital, London. Published work includes: with R. L. Cooper, "3 : 4-Benzpyrene and other polycyclic hydrocarbons in cigarette smoke" (*Brit. J. Cancer*, 1955, 9, 304); with J. A. S. Gilbert, "Polycyclic hydrocarbons in tobacco smoke: pipe smoking experiments" (*Brit. J. Cancer*, 1956, 10, 646); and, with J. M. Campbell, "Polycyclic hydrocarbons in cigar smoke" (*Brit. J. Cancer*, 1957, 11, 192).

Dr R. H. Mole has been working at Harwell since the beginning of radiobiological research work there in 1948. His special interest has been in recovery from irradiation and its delayed effects (see "Quantitative observations on recovery from whole body irradiation in mice", *Brit. J. Radiol.* 1956, 29, 563 and *Brit. J. Radiol.* 1957, 30, 40; "Shortening of life by chronic irradiation: the experimental facts", *Nature*, 1957, 180, 456; and, in collaboration with G. J. Neary & R. J. Munson, *Chronic radiation hazards. An experimental study with fast neutrons*, 1957). Before this, as graduate assistant in the Nuffield Departments of Clinical Medicine and Pathology, Radcliffe Infirmary, Oxford, Dr Mole had an orthodox training in medicine. From 1944 to 1946 he was a pathologist in the Royal Air Force, and in 1947 Clinical Pathologist, Royal Infirmary, Liverpool.

Professor J. W. Orr is Professor of Pathology and Director of Cancer Research in the University of Birmingham, and Honorary Consultant Pathologist to the United Birmingham Hospitals. He is a graduate of the Queen's University of Belfast, and has held the posts of First Assistant Pathologist at St Mary's Hospital, Paddington, London, and Reader in Experimental Pathology in the University

of Leeds. His research work has been mainly concerned with problems of experimental carcinogenesis in the skin, breast, liver, ovary and connective tissue, and with the pathology of human cancer in man. His publications include: "The production of liver tumours by azo compounds" (*Brit. med. Bull.* 1947, 4, 385); "The chemical induction of mammary and ovarian tumours" (*Acta Un. int. Cancr.* 1956, 12, 682); and, with Dr J. G. Jackson, "The ducts of carcinomatous breasts, with particular reference to connective-tissue changes" (*J. Path. Bact.* 1957, 74, 265).

Dr P. R. Peacock is Director of the Cancer Research Department of the Royal Beatson Memorial Hospital, Glasgow. He was trained at Middlesex Hospital, London, where, after qualifying in 1924, he held resident appointments and afterwards research scholarships in the Barnato Joel Laboratories until 1928. His early work was mainly concerned with fat-soluble vitamins and with experimental radiology. He was appointed to his present post in 1928, and in 1933 became the Administrative Medical Officer at the same hospital. He was appointed Honorary Lecturer in Pathology to the University of Glasgow in 1943, and elected a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow in 1944. He was appointed Honorary Treasurer, International Union against Cancer, in 1952. Dr Peacock's published work includes comparative studies of fowl sarcomata induced by chemical carcinogens and of those spontaneous tumours that can be propagated by cell-free extracts (*Amer. J. Cancer*, 1935, 25, 1; *Brit. J. exp. Path.* 1945, 26, 357; *Cancer Res.* 1946, 6, 311). He has made a study of the metabolism of chemical carcinogens and described their natural routes of excretion (*Brit. J. exp. Path.* 1938, 19, 315, 434; *Brit. J. exp. Path.* 1940, 21, 227; *Biochem. J.* 1941, 31, 1276). A paper by Dr Peacock, on the carcinogenic action of heated fats and lipids, was published in *British Medical Bulletin*, 1947, 4, 364. He is particularly interested in dietary factors related to cancer of the alimentary tract. He holds the view that much human cancer could be avoided, and that closer co-ordination of clinical, statistical and experimental research may lead to identification of some avoidable forms of cancer.

Dr M. H. Salaman was trained at Cambridge and the London Hospital. After qualification he studied the antigenic structure of vaccinia under Professor S. P. Beeson and later Sir John Ledingham. In 1939 he entered the Cancer Research Department of St Bartholomew's Hospital, and except for three years as a pathologist in the Royal Army Medical Corps, during which he studied serum hepatitis and was able to recommend measures for its prevention, he has continued to work on cancer. He came to the London Hospital in 1946, and was appointed Director of the Cancer Research Department there in 1948, a post which he still holds. He has been mainly interested in the mechanism of carcinogenesis and particularly in the action of "incomplete carcinogens", i.e., agents which can bring about part but not the whole of the process of tumour production. Three representative publications are: "The combining properties of vaccinia virus with the antibodies demonstrable in anti-vaccinial serum" (*Brit. J. exp. Path.* 1937, 18, 245); with D. E. Lea, "Experiments on the inactivation of bacteriophage by radiations, and their bearing on the nature of bacteriophage" (*Proc. Roy. Soc.* B, 1946, 133, 434); with F. J. C. Roe, "Incomplete carcinogens: ethyl carbamate (urethane) as an initiator of skin tumour formation in the mouse" (*Brit. J. Cancer*, 1953, 7, 472).

Dr Regina Schoental is a member of the Scientific Staff of the Medical Research Council's Toxicology Research Unit at Carshalton, Surrey, England. Before this she had worked on behalf of the British Empire Cancer Campaign at the Sir William Dunn School of Pathology, Oxford; at the Chemistry Department, University of Glasgow; and at the Cancer Research Department, Royal Beatson Memorial Hospital, Glasgow—with the exception of a year spent in the USA (1952-53). She has studied, among other problems, the carcinogenic constituents of coal-tar and shale-oil, and the metabolic and chemical oxidation of polycyclic aromatic hydrocarbons, and she has synthesized some of their phenolic metabolites. Since the discovery of the carcinogenic activity of pyrrolizidine alkaloids for the rat liver, Dr Schoental has been mainly interested in the mechanism of their action, and in the role medicinal plants containing these alkaloids may play in the causation of liver disorders in some parts of the world. Her published work includes: "The oxidation of aromatic rings by purely chemical means" (*Symp. biochem. Soc.* 1950, 5, 3); "Kwashiorkor-like syndrome and other pathological changes in rats as a result of feeding with *Senecio* alkaloids (isatidine)" (*Voeding*, 1955, 16, 268); and, with J. W. Cook & E. Duffy, "Primary liver tumours in rats following feeding with alkaloids of *Senecio Jacobaea*" (*Brit. J. Cancer*, 1950, 4, 405).

Dr A. L. Walpole is a graduate of London University and a member of the research staff of Imperial Chemical Industries Limited (Pharmaceuticals Division). Since 1942 his chief work with that firm has been concerned with cancer chemotherapy and chemical carcinogenesis. With other members of a research team he discovered tumour-inhibitory properties in alkylating agents containing methylolamide, epoxide and ethyleneimine groups and later investigated the carcinogenic potentialities of compounds of this type. These researches are described in a series of papers written in collaboration with J. A. Hendry, R. F. Homer, D. C. Roberts & F. L. Rose: "Cytotoxic agents: I, Methylolamides with tumour inhibitory activity, and related inactive compounds; II, Bis-epoxides and related compounds; III, Derivatives of ethyleneimine; IV, The carcinogenic actions of some monofunctional ethyleneimine derivatives" (*Brit. J. Pharmacol.* 1951, 6, 201, 235, 357; 1954, 9, 306). With M. H. C. Williams & D. C. Roberts, Dr Walpole first described the carcinogenic activity of 4-aminodiphenyl (*Brit. J. industr. Med.* 1952, 9, 255). He is currently engaged in a systematic investigation of the carcinogenic properties of aromatic amines derived from diphenyl and stilbene respectively.

Dr M. H. C. Williams is the Division Medical Officer to the Dyestuffs and Pharmaceuticals Division of Imperial Chemical Industries Limited, which he joined in 1948. Before taking up this post he was working with the Medical Research Council's Pneumoconiosis Research Unit in South Wales. For eight years, with his colleague Dr A. L. Walpole, he has been carrying out a systematic study of the carcinogenic effects of substituted aromatic amines. His publications include: a paper on the discovery, with Dr Walpole, of the carcinogenic effect of 4-aminodiphenyl (xenylamine) ("Tumours of the urinary bladder in dogs after ingestion of 4-aminodiphenyl", with A. L. Walpole & D. C. Roberts, *Brit. J. industr. Med.* 1954, 11, 105); with T. S. Scott, "The control of industrial bladder tumours" (*Brit. J. industr. Med.* 1957, 14, 150); and a chapter on occupational tumours of the bladder in the forthcoming volume III of *Cancer*, edited by R. W. Raven.

Dr Dennis Leyton Woodhouse graduated in chemistry at the University of Birmingham in 1922; he obtained his M.Sc. in 1923. From 1924 to 1930 he held the appointment as Sir Charles Hyde Research Fellow to the Joint Board for Research in Mental Diseases, City and University of Birmingham. He took his Ph.D. in 1930. Dr Woodhouse secured the post of Research Officer to the Birmingham Branch of the British Empire Cancer Campaign in 1931. He was elected a Fellow of the Royal Institute of Chemistry in 1947, and has been Reader in Chemical Pathology (Cancer Research) in the Department of Pathology, Medical School, Birmingham, since 1954. He has published papers, in the *Biochemical Journal*, *Cancer Research*, *British Journal of Cancer*, *Journal of Pathology and Bacteriology*, on chemotherapy of cancer and aspects of carcinogenesis.