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 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. Metal objects are dipped in alkaline dichromate to produce a coating of Al oxide 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 Loken (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_2S_3, with small amounts of Au, Ag, and Pt.

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

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.

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 2,460 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 Butt & 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)[1], 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

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