FILE NAME: Celanese (CEL)

DATE: 1958

DOC#: CEL054

DOCUMENT DESCRIPTION: Laubly Exhibit #7 – Medical Journal

THE PRACTITIONER

Edited by

SIR HENEAGE OGILVIE
K.B.E., D.M., M.Ch., F.R.C.S.

WILLIAM A. R. THOMSON, M.D.

JOSEPH GARLAND, M.D.

Vol. 181

July—December 1958

THE PRACTITIONER
5 BENTINCK STREET, LONDON, W.1
1958

oniosis panels who review each certified case at stated intervals—usually ie or two years. If the general practitioner is to be successful he must ave a working knowledge of the legal and administrative arrangements for isablement and death benefits: an excellent series of pamphlets in non-le gal language is available at offices of the Ministry of Pensions and National surance. I would particularly underline that, save in exceptional circumances, a death claim is dependent upon a post-mortem examination. lence the need immediately to advise the pneumoconiosis panel or H.M. oroner so that the examination can be arranged with as little upset to the ependants as possible.

GENERAL CARE

he care of pneumoconiosis cases is very similar to that of cases of chronic ronchitis and emphysema, with, in severe cases, a tendency to congestive eart failure. In silicosis cases particularly, the general practitioner must be igilant for possible active tuberculosis. Once a patient has been diagnosed s pneumoconiosis there is a tendency to ascribe all his ills to the dust. neumoconiosis does not confer immunity to other diseases and so the octor must be alert to recognize and treat promptly any intercurrent disease. would plead that consultations should not be hurried; allowing time to sten will achieve the most important items of therapy: support and ncouragement. Medicines should be prescribed sparingly, and then only f the simplest kind.

Finally, a word about certificates: be honest and factual. And remember hat the decisions of the pneumoconiosis panels are based upon the law as it s—justice within the law—and not on what you or I think it ought to be.

CONCLUSION

t is improbable that in the near future we shall see any radical alteration f the existing National Insurance (Industrial Injuries) Act. This being so, here are certain matters concerning pneumoconiosis which demand urgent ttention by the Ministry of Pensions and National Insurance:—

(1) Whether disabling bronchitis and emphysema is an occupational lisease in certain industries and occupations.

(2) The need for less formal and more informative reports by the pneumoconiosis panels to general practitioners and employers in all cases requiring their cooperation.

References

Jones, W. W. (1952): 'Tuberculosis in Industry', National Association for the Prevention of Tuberculosis, London.

Sutherland, C. L. (1956): *Trans. Ass. industr. med. Offrs*, 6, 103.

OCCUPATIONAL CANCER

By M. W. GOLDBLATT, C.B.E., M.D., M.R.C.P.
Institute of Cancer Research, Royal Cancer Hospital

SINCE I last reviewed this subject in *The Practitioner* (Goldblatt, 1950) a great deal of work has been carried out which has extended our knowledge not only of the industrial carcinogenic agents then known, but also of the importance which must be attached to a constant awareness of the probability of new or even old industrial agents inducing tumours in man.

MODE OF ABSORPTION OF OCCUPATIONAL CARCINOGENS

Once an occupational carcinogen has been recognized as existing in an industry, its mode of entry into the organism must be considered immediately because there is bound to be a considerable time-lag before its elimination or inactivation or before improved protective measures can be operated. The simple formula that manufacture or use must cease immediately is seldom practicable.

The recent cases of demonstrable clinical bladder carcinogenicity of a rubber anti-oxidant containing a significant proportion of unreacted β-naphthylamine led to the immediate cessation of manufacture and use of the preparation. But this will not be followed by immediate cessation of cases attributable to exposure to it; hence, follow-up and cytological examination of all men who were exposed is now going on and should continue throughout their lives. Similar action was taken in the United States in respect of an aromatic amine—4-amino diphenyl or xenylamine—which was found to be carcinogenic, although the rubber anti-oxidant manufactured by condensing it with an aliphatic ketone has, after several years' experiment, not been found to be hazardous.

It is now common knowledge that toxic substances in industry may be absorbed by all the available routes, most frequently by inhalation, very often *per cutem* and relatively rarely by mouth. In certain operations absorption can occur by the conjunctiva. Absorption from the mucous membranes of mouth and nose is an infrequent occurrence but has occurred in laboratories. In industrial conditions combinations of routes of absorption arise depending upon the physical properties of the materials involved.

Inasmuch as many of these are insoluble in water and in lipoids we must envisage phagocytic action in the lung and later deposition in the affected areas; for the more soluble materials, greater mobility and effects at remoter areas may be anticipated. The relation between ultimate deposition and retention in the affected areas is by no means easy to describe: no single mode of action on the relevant cells seems possible except in terms of as yet obscure energy transferences, or potent alternative attacks on the cell structure or cell internal economy. For most of the materials it is not pos-

ble as yet to lay down environmental concentrations and total periods of exposure which might be held to determine the development of malignant change.

PERCUTANEOUS PENETRATION

enetration of the skin may occur either through cellular layers or at the rifices of the sebaceous glands.

Aromatic amines.—All occupational carcinogenic aromatic amines are poid-soluble solids but, according to circumstances, can penetrate through ie skin when applied to it as dust, in a molten state or as hot fumes—most asily when molten. The probability is that they are absorbed mainly rough skin apertures.

Radiation.—For the energy of radioactive particles or electro-magnetic aves to produce pathological effect, it must be absorbed by the tissues ffected. The precise way in which the energy thus absorbed leads to cellular hanges is the subject of much theorizing but, so far as malignant disease is oncerned, it seems probable that there occurs a physical and chemical hange in the chromosome make-up (chromosome breaks; rejoining in bnormal ways; changes in nucleic acid or nucleoprotein in the nucleus; utagenic action) which irreversibly sets the previously normal cell on the ourse of malignancy. Soft radiations are absorbed by skin cell layers. More enetrating radiations (harder radiation) will pass through the skin layers and ffect organs and tissues according to their radiosensitivity. Some tissues re very sensitive, others are relatively insensitive. In regard to neoplastic lisease, the skin is one of the sensitive tissues, by virtue of the damage and lestruction produced by radiation in sufficient dose (wave-length, duration, ntensity, total dose) and the subsequent ingrowth from less damaged adacent areas of epithelial cells which have absorbed sufficient energy to cross he line of normality to malignancy. Lymphatic tissue (anomalous in some espects), blood-forming tissue, germinal epithelium, and intestinal mucosa ire in a truer sense radiation-sensitive tissues, whereas the more stable issues, e.g. liver, pancreas, kidneys, muscle, connective and nervous tissue, ire much less affected by radiations. The general view is that tissues in vhich much 'turn-over' of cells takes place, are more radiation-sensitive han other more static tissues. 'Turn-over' in this context is synonymous vith 'mitotic replacement'. Radiation sensitivity means greater than normal endency to respond to a dose or doses of radiation by cellular degeneration ir chemical and metabolic aberration.

The modern conception is that a chemical carcinogen penetrates into the skin and is metabolized. This metabolic process entails the liberation of energy which is absorbed by the germinal layer of the skin until a critical level is reached at which the cells become malignant. This energy-transference view of carcinogenesis has the virtue of bringing the picture of this process into ire or less familiar background. It may also be that small

amounts of radiation or chemical energy applied appropriately to a cell may render it more susceptible to endogenous completion of the carcinogenic process. Some animal experiments give support to such a co-carcinogenic action by radiation. It is obvious that a cell change which leads to malignancy must be one which is compatible not only with survival but also with independence, enhanced power to multiply, resistance to normal inhibitions of growth and competitive superiority over normal cells.

Tumour-cell nuclei are abnormal not only in morphology and staining properties, but also in the mitotic process. An enhanced rate of multiplication, however, does not mean that all phases of mitosis are accelerated. Thus, in tissue culture, tumour cells show a retardation of metaphase.

INGESTION OF CARCINOGENS

This involves absorption from the gastro-intestinal tract, including the oral mucous membrane.

Radioactive paints.—Ingestion of carcinogenic agents in industry is, on the whole, an unusual factor, the only well-authenticated case being that of luminizers, with which, following deposition of radioactive compounds in the bones, there follow blood diseases and osteosarcoma. Absorption probably occurs from the oral mucous membrane, as well as from the gut, as a result of 'pointing' the paint brushes with the lips. The use of pens instead of brushes largely eliminated the practice and in this country the stringent 'luminizing order' incorporated into the Factories Acts has led to a full realization of what is involved.

Aromatic amines.—In former times—say, 25 years and more ago—it is certain that many of these solid compounds were taken in *orally* as dust and fume. It is impossible to say what proportion of the carcinogenic action was attributable to absorption by this route. In modern conditions of manufacture and use (Scott and Williams, 1957) it is reasonably certain that this route of absorption is not significant, but testing of the mouth and saliva for free amines of workers would be of interest, especially at those locations where the final solid product emerges and is weighed into drums. This would, of course, only be relevant where the processes of manufacture of carcinogenic bases are still in operation.

I now propose to consider a few occupational carcinogens in greater detail.

ASBESTOS

In his report for 1955 the chief inspector of factories has extended his data on the association of asbestosis and cancer of the lung by pointing out that between 1924 and 1956, 22 per cent. of 222 men and 12 per cent. of 143 women had the combined disease, thus demonstrating an increasing incidence of association. Such an association does not occur in silicosis (Goldblatt and Goldblatt, 1956; Gloyne, 1951; Meiklejohn, 1956). Werber (1952) found that carcinoma of the lung occurs in up to 17 per cent. of cases of asbestosis, with an induction time of 1½ to 20 years.

Doll (1955) studied the post-mortem and occupational data of 105 consecutive eased workers in a single large asbestos works, of whom 75 had asbestosis; of latter, 15 had associated cancer of the lung, of the remaining 30 without asbes- s three had also cancer of the lung. In 1931, the asbestos industry regulations re issued and in this particular factory it could be reckoned that it was not until 33 that they became effective. In all 15 cases of asbestosis cancer there was a tory of the individual having worked in the industry for from 9 to 23 years prior 1933, but there was no case among those who had entered it between 1923 and 33. The mortality data of 113 men with 20 years in the factory yielded 11 cases of combined disease and none with lung cancer without asbestosis.

Doll (1953) points out that such an incidence is about 10 times that pected in England and Wales and far exceeds that of silicotic miners blished over 30 years ago by the South African Miners Phthisis Medical reau—0.7 per cent. for silicotic miners; 0.7 per cent. for non-silicotic ners and 0.9 per cent. for European male surface men. Agreement as to association between asbestosis and lung cancer was reached at the ernational symposium on the endemiology of lung cancer (1953), Wyers 949), having already stated that the oat cell and columnar cell types were most frequent. Hunter's (1955) belief that the malignant tumour appears ny years after exposure to asbestos has terminated, is not borne out by ll's data on the 15 cases referred to: six in less than one year, three in one ar, three in three years, two in eight years, and one in thirteen years *after sation of exposure.*

These tumours are very malignant and soon become fatal; so we must ppose that, whatever the mechanism of cellular change, it requires a very ng induction time to reach the tumour state. The interesting suggestion is ade by Bonser *et al.* (1955) that silica is the common factor in the en- onmental exposure of the asbestos worker and the hæmatite miner and at, in both, the fibrosis precedes the malignant change in the lung. They ceive the asbestos and the hæmatite (iron oxide) as somehow converting fibrogenic action of silica into a carcinogenic action. King *et al.* (1946) re able to induce peribronchiolar fibrosis in rabbits exposed to asbestos re dust; but when the fibre was reduced to dust by fusion and grinding, fibrosis followed long exposure to it. Lung cancer in animals, however, s not hitherto followed exposure to asbestos or to brucite (crystalline) hich also induces peribronchiolar fibrosis although it contains only 0.9 per nt. SiO_2 as silicate, whereas chrysotile (the most used of the fibrous sili- tes) contains over 40 per cent. SiO_2 as silicate when mined.

The clinical problem is difficult since Doll found three cases of lung ncer without asbestosis, after such short periods of exposure as two, nine d seven years. Knox and Beattie (1954), who have had much direct perience of the asbestos industry and its hazards, regard the malignant anges in such cases as due to asbestos as such or to asbestos bodies and eir decomposition products; in their view the fibrosis would require a uch longer time. The observations of Gloyne and of M. J. Stewart, of eds, that the is a gradual dissolution of asbestosis bodies and fibres the lung is mmed by Knox and Beattie and the view upheld that the

lesions induced by the decomposition products survive the fibres. Champeix and Bouteville (1950) applied electron microscopy (magnification 25,000) to asbestosis bodies and, using micromanipulation, obtained appearances which seemed to indicate the gradual solution of the fibre located in the asbestosis body. Knox (1955) regards the slowly disintegrating asbestosis bodies as yielding a product which acts upon the already chronically irritated and, probably, abnormal epithelium. This is, of course, based upon the location of the asbestosis body in the alveoli and the connective tissue in the asbestosis lung and upon the evidence of irritation given by the thickened, compressed alveolar walls. Although British authorities are probably inclined to accept asbestos or asbestosis as strongly influencing the tendency to malignancy, it must be kept in mind that until quite recently Lynch (1956) considered the evidence as inconclusive but worthy of extension and further investigation. In this field, as elsewhere, the great need is for a reliable experimental method for the induction and study of pulmonary carcinogenesis.

HÆMATITE

Hæmatite mining is associated in varying degree with the presence of free silica and in the last twenty-five years it has become increasingly clear that silicosis is a hazard in this industry, especially since the introduction of mechanical drilling and blasting methods produced a lot of dust. Some 20 years ago in the Cumberland mines there was a certain amount of confusion on the silicosis hazard because a good many miners had formerly worked on the Rand and because of the use of the term 'siderosis'. In the period 1930-35, 48 hæmatite miners were certified as having died from silicosis and silico-tuberculosis. As regards etiology such cases fit in with foundry workers and grinders who have been exposed to both iron and silica.

The old experimental finding of Kettle (1932) that a thin layer of iron oxide over quartz particles prevents the development of silicosis in animals is not relevant to the hæmatite problem because here the silica particles are free and associated with, but *not* coated by, iron oxide and do induce silicosis but perhaps in some modified way which seems to predispose to the later development of carcinoma of the lung. Thus, Faulds and Stewart (1956) report that in the six-year period, 1948-53, 15 per cent. of 89 consecutive necropsies of hæmatite miners showed cancer of the lung and the tumours were usually located in the areas of fibrosis—due to sidero-silicosis, so-called by Stewart because of the amount of silica present in the lungs of these workers, and to distinguish the condition from the benign pulmonary siderosis seen, for example, amongst iron and steel welders after years of work in confined ill-ventilated spaces.

Investigation of the health of arc-welders, even those who used welding rods (electrodes) containing silicates, carbonates, fluorides and [illegible]r compounds, has not revealed any effect on health and this appl[illegible] those

rkers who showed x-ray evidence of siderosis, reticulation or nodulation *t no fibrosis*. The condition is slowly reversible when welding is left, the n oxide lying inert for years (Doig and Duguid, 1951).

It may be recalled that Kennaway and Kennaway (1947) found no in- ase in cancer rate among workers exposed to a silicosis risk, except in the e of metal-grinders; this was confirmed by Turner and Martin (1949) o found that 60 per cent. of cancer deaths among silicotic grinders were e to cancer of the lung. Doll (1953), however, does not accept silica as the nificant factor in the development of the lung cancers and leaves it to me other specific industrial hazard' but without any suggestion as to what s might be.

Policard and Collet (1952) found deposits of silica in the lungs of the ert inhabitants of North Africa (in the peri-bronchial and peri-arterial aths: i.e. the same locations as characterize coal particles in anthracosis l ferric oxide in siderosis), but no evidence of silicosis. Desert fine sand is ocuous both clinically and experimentally. Policard and Collet point out t desert sand always contains ferric oxide and it may be that this is the son for its innocuousness, as would have been held by Kettle. The rnative explanation of 'old' sand as opposed to freshly fractured silica st also be kept in mind. It would be of great interest to know the in- lence of pulmonary cancer among desert people. Clinical and experimental idence all points to the inertness of iron oxide.

In reference to both asbestos and hæmatite the position is summed up as lows by Bonser *et al.* (1955):—

> It seems possible, therefore, that the fibrous nature of asbestos or the presence hæmatite dust may exert a modifying effect on the chemical action or on the otic process itself. . . . it is suggested that this (silica) may be the carcinogenic nt. The presence of silica (as silicic acid) causes pulmonary fibrosis which cedes the malignant process. The fibrosis is usually of lesser degree, however, in se lungs in which cancer supervenes. On published evidence the case for an logic relationship between nodular silicosis *per se* and lung cancer is much less ng than in silicosis associated with siderosis and in asbestosis'.

NICKEL

e problem of the cause of the remarkable tumours of the ethmoids and the lung among workers engaged in the carbonyl process for the refining nickel was briefly dealt with by Goldblatt (1950) and in greater detail by ldblatt and Goldblatt (1956). The condition is a 'prescribed disease' der the National Insurance (Industrial Injuries) enactment and is defined (1) Carcinoma of the mucous membrane of the nose and associated air uses and (2) primary carcinoma of a bronchus or of a lung; the carcinogen ng defined as 'nickel produced by the decomposition of a gaseous nickel mpound'.

In the period 1923-50, 52 cases with 49 deaths from cancer of the nose d 93 cases with 90 deaths from cancer of the lung were reported in the 50 Report of chief inspector of factories. The mean induction times

were 23 and 25 years respectively and all the cases arose in the same nickel-refining works. In spite of the rarity of cancer of the ethmoids and of this high incidence in a single works operating a single refining process, Bonser *et al.* (1955), with all the weight of their authority, are doubtful of its industrial origin and state that there is no experimental support.

The indictment in the official definition is really of a process rather than of a substance and it may be that Bonser and her colleagues are implying that nickel is doubtful as a carcinogen. Certainly, nickel in its ordinary applications is not to be regarded as a carcinogen or as offering a hazard of this kind to the very many people who are skin-sensitive to nickel-plated articles. Finely divided nickel, however, such as would be deposited from the decomposition of inhaled small volumes of nickel carbonyl, would have properties different from those associated with the bulk metal. Further, finely divided nickel absorbs gases, catalyses hydrogenations and is easily oxidized in the air and may, perhaps, form significant compounds with tissue proteins and enzymes. The ethmoid sinuses are under slight negative pressure; nickel carbonyl is quickly decomposed in the tissues and finely divided nickel could thus be deposited and immobilized in the very thin mucous membrane, extremely closely applied to the bone. A measure of œdematous stenosis at the fine orifices which connect the sinuses to the nasal meatuses could accentuate the process of retention. Barnes and Denz (1951) found that severe and extensive fibrosis often followed exposure of rats to nickel carbonyl, an observation which must be considered of great significance in the elucidation of the cancer hazard.

In the industrial electrolytic refinement of nickel, in which no carbonyl is formed, no cases of ethmoid or nasal tumours occur in this process but five cases of bronchogenic carcinoma were discovered by Loken (1950) in a single factory operating this process in Norway. The lung of one of these cases analysed eight years after cessation of exposure still contained some 1 mg./g. nickel.

The whole question is very complicated and cannot be pursued further here, except to say that continued observation of workers, past and present, in the carbonyl process is proceeding. The occasional case of nickel carbonyl poisoning still reported may perhaps yield new cases of the old disease. The older arsenic theory of causation is not acceptable and the officially accepted nickel and nickel carbonyl theory is not finally decided.

'ISOPROPYL OIL'

In 1950, in a chemical factory in the United States, seven cases of tumour of parts of the respiratory tract—lungs, paranasal sinuses, vocal cords—were discovered. The ages at death in three cases were 31, 36 and 41 years, and the periods of exposure to a particular process were from 6 to 16 years. The process was theoretically a relatively simple one for the manufacture of isopropyl alcohol.

The process was a catalytic hydration of the gas, propylene, as follows:—

$$CH_3.CH = CH_2 + H_2SO_4 \rightarrow CH_3.CH.CH_3 \xrightarrow{Hydrolysis} (CH_3)_2.CH(OH) + H_2SO_4$$

$$\qquad\qquad\qquad\qquad\quad | \qquad\qquad\qquad\qquad\qquad\quad |$$

$$\qquad\qquad\qquad\qquad OSO_2OH \qquad\qquad\qquad\quad +$$

Propylene — Intermediate compound — Isopropyl alcohol

This is the basal reaction sought, but the technical impurities of the propylene led to many other undesired products; e.g. isopropyl ether, sulphur dioxide, and an oily product called 'isopropyl oil' for want of more specific information about it. A high-boiling petroleum residue was used as a heat transfer agent and also as an anti-foaming additive. Leaks of the isopropyl oil on concentrating produced a brown tar; in addition, a black tar of carbonaceous matter formed on the isopropanol-sulphuric acid solution, which had to be removed before recycling to increase the concentration of the alcohol. No arsenic or nickel or iron oxide was present at any stage of the process and the acid fume was not under suspicion.

From a consideration of all the products available, both from the occupational and experimental points of view, Weil *et al.* (1952) concluded that the isopropyl oil was the most likely carcinogen. This would seem to imply a potent volatile hydrocarbon, but its nature is not known. The conditions might promote some epoxide formation, but one hesitates to suggest more without greater information about the process. It may be recalled that the di-epoxides are among the more suspicious cytotoxic agents. The process is now discarded. But it would be most instructive to trace so subtle a carcinogen as must have been present somewhere in the reaction.

CHROMIUM

Although the association of carcinoma of the lung with the manufacture of chromates is widely recognized, the nature of the carcinogen is not known.

In 1952, Brinton *et al.* published an analysis of the morbidity and mortality data of sick benefit associations in the United States. They found the cancer mortality among chromate workers to be 4.5 times the expected rate, whilst that for respiratory cancer was 29 times the expected rate. A radiological and clinical examination of 897 chromate workers in six factories (Public Health Reports, 1952) revealed 10 cases (7 white; 3 coloured) of bronchogenic carcinoma. The induction time varied from eight to 39 years, whilst the ages ranged from 40 to 50 (whites) and from 53 to 62 (coloured). Seven of the ten patients had perforated septa.

In 1944, Bidstrup (1951) carried out a radiological survey of 724 workers in the chromate industry in Britain. She found only one case of lung cancer, as opposed to an expected incidence of 0.4. Some six years later, Bidstrup and Case (1955) found that 59 of these 724 workers had died and that in 12 cases the cause of death had been given as lung cancer. In addition, two of the workers still alive were known to have cancer of the lung. Using the method of comparative composite cohort analysis, the expected number of deaths from lung cancer was found to be 3.3, as opposed to the discovered 12 cases. The calculated probability against this difference being due to chance was 200 to 1. There was no evidence that factors such as social class, place of residence, or smoking habits had any effect, and it was therefore concluded that a real risk of lung cancer exists in the chromate industry, the interim figure being 3.6 times the mean corrected risk in the general population.

There is still no agreement as to the carcinogenic form of chromium. Some hold that it is the hexavalent form—chromate or dichromate. Others contend that it is the trivalent form as it is found in the ore. The great lack so far has been the inability to demonstrate carcinogenicity in the experi-

PITCH, TAR, SOOT AND MINERAL OILS

The presence of identifiable skin carcinogens in pitch, tar and soot is now well established, although there may be more present than have as yet been identified. With the widespread and increasing use of mineral oils not only as lubricants but also as 'cutting oils' for high-speed tooling, the possible carcinogenicity of the latter has been extensively investigated, having regard to the unavoidable spraying and splashing that contaminate the operatives. Since 'cutting oil' formulations contain surface-active agents (emulsifiers), rust-inhibitors, disinfectants and other materials designed to meet special requirements, these also have to be considered. The extensive work of Twort and his colleagues between 1928 and 1939 showed that the most carcinogenic of the mineral oils was shale oil, but none was as potent as tar. Since shale oil is a manufactured oil, however, its potency is more properly compared with cracked petroleum oils than with the naturally occurring petroleum oils which generally are of low potency.

In three factories using high speed coolants Cruickshank and Squire (1950) found that one-third of 138 workers had hyperkeratoses and warts, liability to these affections increasing with length of service—another example of the proposition that it is length of exposure rather than intensity which determines the mean induction time of the tumour. Cruickshank and Gourevitch (1952) found from the hospital records in Birmingham that of 37 cases of cancer of the hand and forearm (1941-50) and 34 cases of cancer of the scrotum (1940-48), 30 derived from a population of 88,859 metal workers and 41 from the remaining population of 271,000 (population figures of 1931). Experimental evidence of skin carcinogenicity led Cruickshank and his colleagues to regard cutting oils as significant hazards and to foretell that as the years pass more and more cases will come to light.

In Canada, Mastromatteo (1955) found six cases of squamous carcinoma of the skin and one of a wart in a single machine shop; Gilman and Vesselinovitch (1955) painted used, unused, diluted and undiluted cutting oil formulations on two strains of mouse and induced high proportions of malignant tumours—so high, indeed, that they are inclined to cast suspicion on the unrevealed additives in the soluble cutting oils. They also found that tumours of very long induction time were induced even with high dilutions, if a strain of mice was used which is hardy, long lived and toxicity resistant.

In connexion with the testing of any oil formulation, it is clear from the work of Hieger and Woodhouse (1952) that 'it is unsatisfactory to exclude carcinogenicity on the basis of tests on mice only', since they found that rabbit skin reacts to oil fraction carcinogens better than does mouse skin. Unfortunately, specific determinations of the carcinogens in mineral oils is not yet possible, and biological testing for carcinogenicity is likely to continue for a long time yet. Certain compounds have been isolated in small amounts from mineral oils and found to be carcinogenic to mouse skin. The following two compounds have been known as carcinogens for a long time: (a) 6-isopropyl-1.2-benzanthracene, which produces epitheliomas and warts on mouse skin; (b) 4-, 5-, 6-, methyl chrysenes, which produce local sarcomas on subcutaneous injection. They have also been shown to be present in a high-boiling catalytically cracked petroleum.

Fisher (1957) has recently reopened the question of the relation between age at entry into a 'carcinogenic occupation' and the development of tar-

warts. From his records in the gas industry, he tends to the view that the higher the starting age the sooner will the warts appear and the greater will be the susceptibility, as measured by the numbers which develop. He appears to hold that carcinogenic tars have an ageing effect on the skin, with the resulting greater tendency to develop squamous epithelioma possessed by the skin of old people. Animal experiments do not support such a view and to establish it in man requires an analysis of a very large series of cases. Old skin is thinner, less elastic, more or less atrophic, with less subcutaneous fat, fewer sweat glands, less sebaceous secretion and more liability to lose protective mechanisms against exogenous irritants. In regard to the latter point, it is common experience in the chemical industries to find that after many years of skin resistance to particular irritants, there is a sudden breakdown in the barrier with the development of marked sensitization. This, however, may occur many years before any manifestation of senility of the skin is apparent. It is perhaps permissible to suppose that with increasing years there is a diminishing ability of the epidermis to metabolize both exogenous carcinogens and external irritants, or there may be a loss of some compound which can combine with such substances and inactivate them.

AROMATIC AMINES

The carcinogenic aromatic amines which induce occupational cancer of the bladder, renal pelvis and ureter are beta-naphthylamine, benzidine, 4-amino-diphenyl and alpha-naphthylamine (probably because of its unavoidable content of the beta isomer). There has been so much clinical and experimental study of this subject in the last ten years, that only the outstanding results can be given. For fuller information the reader is referred to the review by Goldblatt and Goldblatt (1956).

Just under sixty years after the first cases were described in Germany in 1895, the disease was prescribed in this country under the National Insurance (Industrial Injuries) (Prescribed Diseases) (No. 2) Regulations, 1953. The official definition is:—

> Primary neoplasm of the epithelial lining of the urinary bladder (papilloma of the bladder) occurring in any occupation involving:—
>
> (a) Work in a building in which any of the following substances is produced for commercial purposes: (i) alpha-naphthylamine, beta-naphthylamine or benzidine or any of their salts; (ii) auramine or magenta.
>
> (b) the use or handling of any of the substances mentioned in sub-paragraph (i) of paragraph (a), or work in a process in which any such substance is used or handled or is liberated.
>
> (c) the maintenance or cleaning of any plant or machinery used in any such process as is mentioned in paragraph (b), or the cleaning of clothing used in any such building as is mentioned in paragraph (a) if such clothing is cleaned within the works of which the building forms a part or in a laundry maintained and used solely in connexion with such works.

Although the disease is described as of the bladder epithelium, it is recognized by the Ministry or its advisers that the tumours may be located in the renal pelvis or in the ureters. This is important because if there is any congenital malformation or other condition which tends to hinder the free

passage of urine from the calyces and pelvis into the ureters ... om the ureter freely into the bladder, the carcinogen may attack the epithelium in those locations. Further, fulguration of the bladder tumour or tumours or partial cystectomy may later be followed by a pelvic or ureteric tumour at a time when the bladder is clear. Moreover, a unilateral renal tumour and nephrectomy can be followed years later, and after cessation of all contact with the prescribed processes, by a renal pelvic tumour in the remaining kidney, without any neoplasms in the bladder.

The occurrence of a non-occupational tumour in a worker who has been exposed to the prescribed processes can rarely be asserted except, perhaps, on the following grounds:

extremely short period of exposure; history of non-occupational disease of the same kind; superlatively good conditions in the factory; location of a primary tumour not in the urinary tract; bladder or renal tumour from other identifiable causes.

Auramine is a diphenylmethane dyestuff; magenta is a triphenylmethane dyestuff. The inclusion of these materials is based upon a statistical analysis of death certificates and other data of the workers in a nominal roll from the principal dyestuff makers in Britain since 1910, who had made auramine or magenta but had had no contact with any of the other substances mentioned in the prescription. It was found that the number of deaths was significantly in excess and the ages at onset and death were markedly less than was to be expected among the general population. Nevertheless, it is not as yet clear what the effective carcinogens are, although there is slight experimental evidence against auramine.

The substances in (a) (i) are bases and it is as base that they constitute the hazard; in the case of benzidine the base character is retained even in the most modern and costly plant; in the case of alpha-naphthylamine an almost automatic conversion to an innocuous compound is effected, but some base may still be necessary; for beta-naphthylamine a process is available which eliminates all carcinogenic hazard.

The word 'liberated' arose from the use in the rubber industry of an anti-oxidant which contained a small proportion of free beta-naphthylamine, the latter being liberated during the process of vulcanization of the rubber articles. The result, over a period of years, was a considerable number of bladder cancer cases among the rubber workers. In the United States a compound similar to benzidine, 4-amino-diphenyl, was manufactured for a number of years and used for the preparation of a rubber anti-oxidant. This compound has since been found to be a powerful carcinogen and has led to a high proportion of bladder cancers. Since the amine was not free in the anti-oxidant, no cases of bladder cancer arose among the rubber workers or among dogs to which the material was fed.

In former times laundrymen were in hazard when they dealt with the heavily contaminated working clothes of process men, and developed bladder tumours. Nowadays very high-grade laundries are installed in the factories and the small amount of contamination, if any, of the suits of working

thes issued to the process men should offer no danger to the laundrymen.

CARCINOMA OF THE BLADDER

c attack on the bladder is made by metabolic products of the prescribed
stances; this occurs within the bladder, renal pelvis or ureter and not
the blood stream. The effective carcinogens are probably ortho-hydroxy
ivatives of the amines. These are excreted by the dog in the form of
hate ester and other metabolites are present only in minor amounts.
the other hand in man, mouse, rat and rabbit, the patterns of excre-
are similar and quite different from that of the dog. The dog is highly
ceptible to these amines. Man is also highly susceptible, but the rabbit,
ise and rat are not. There is some possibility that the urinary
cursor of the ortho-hydroxy amine is the glucuronic acid conjugate.

much of the most modern work the long-drawn-out feeding experiments with
umed bladder carcinogens has been, in part, replaced by direct implantation
the bladder, the material being incorporated in pellets of suitable non-carcino-
ic vehicles, e.g. paraffin or cholesterol, from which slow diffusion takes place
the bladder wall. Using mice, it has been possible to distinguish the relative
ncies of a great many compounds as bladder carcinogens and to test the possible
ursors of the effective agents. One result of this kind of experiment has been to
w that, on the whole, the primary amines as such are not effective carcinogens;
not all are completely inactive.

Methods for detecting carcinogenic properties (e.g. oral, implantation,
-painting, subcutaneous injection) all rest on the belief that a positive
lt in animals should be interpreted as indicating actual or potential
cinogenicity in man. There are many dilemmas in this, not the least of
ch are the vastly varying susceptibilities of different species and tissues.
l there been no dogs in the world, there would still be much argument
ut the bladder carcinogenicity of these amines, until a significantly
onsive animal had been found, to which man then would have been
ated. This point is mentioned here because of the apprehensions felt
adays about food additives of very different kinds. If, for example, a
l colour produces a local tumour on subcutaneous injection, or if it can
metabolized by animals to yield a carcinogenic amine, or if it induces
aplasia or neoplastic change on implantation in the bladder of mice or
vagina of rats it is at once condemned and expunged from the proposed
mitted list of food colours. We cannot but subscribe to such a decision
what it means in terms of man is not a question one should expect to be
wered.

rising out of the ortho-hydroxy amine theory of occupational bladder
cer, a suggestive hypothesis has been proposed for the etiology of non-
upational bladder tumours. Fishman and Anylan (1947) found that
man cancer tissue possesses greater glucuronidase activity than normal
ue adjacent to it. Boyland *et al.* (1955) found that the urine of patients
h cancer of the bladder possesses notably increased sulphatase and
curonidase activity and anticipated the later finding by Boyland and
lliams (1956) such urine contains much more of certain metabolites

of the essential amino-acid, tryptophane, than normal urine. Thus, whereas the normal daily excretion of 3-hydroxy anthranilic acid is about 30 mg., the bladder cases excrete up to about 150 mg. This, and some other metabolites of tryptophane, were found by Boyland and Watson (1956) to induce carcinoma of the bladder. This is the first suggestive proposal as to the etiology of so-called spontaneous bladder tumours in man.

References

Annual Report of the Chief Inspector of Factories for 1955. (1956): H.M. Stationery Office, London.
Barnes, J. M., and Denz, F. A. (1951): *Brit. J. industr. Med.*, 8, 117.
Bidstrup, P. L. (1951): *Ibid.*, 8, 302.
——, and Case, R. A. M. (1955): *Ibid.*, 13, 260.
Bonser, G. M., Faulds, J. S., and Stewart, M. J. (1955): *Amer. J. clin. Path.*, 25, 126.
Boyland, E., Wallace, D. M., and Williams, D. C. (1955): *Brit. J. Cancer*, 9, 62.
——, and Watson, G. (1956): *Nature (Lond.)*, 177, 837.
——, and Williams, D. C. (1956): *Biochem. J.*, 64, 578.
Brinton, H. P., Frasier, E. S., and Koren, A. L. (1952): *Pub. Hlth Rep. (Wash.)*, 67, 835.
Champeix, J., and Bouteville, J. (1950): *Arch. Mal. prof.*, 11, 607.
Cruickshank, C. N. D., and Gourevitch, A. (1952): *Brit. J. industr. Med.*, 9, 74.
——, and Squire, J. R. (1950): *Ibid.*, 7, 1.
Doig, A., and Duguid, L. N. (1951): 'The Health of Welders', H.M. Stationery Office, London.
Doll, R. (1953): *Brit J. industr. Med.*, 2, 521.
—— (1955): *Ibid.*, 12, 81.
Faulds, J. S., and Stewart, M. J. (1956): *J. Path. Bact.*, 72, 353.
Fisher, R. E. W. (1957): 'Proceedings of the International Congress on Occupational Health', Helsinki, vol. 3, p. 402.
Fishman, W. H., and Anylan, A. J. (1947): *Cancer Res.*, 7, 808.
Gilman, J. P. W., and Vesselinovitch, S. D. (1955): *Brit. J. industr. Med.*, 12, 244.
Gloyne, S. R. (1951): *Lancet*, I, 810.
Goldblatt, M. W. (1950): *The Practitioner*, 164, 404.
——, and Goldblatt, J. (1956): 'Industrial Medicine and Hygiene', edited by E. R. A. Merewether. London, vol. 3.
Hieger, I., and Woodhouse, D. L. (1952): *Brit. J. Cancer*, 6, 293.
Hunter, D. (1955): 'The Diseases of Occupations', London.
International Symposium on Endemiology of Lung Cancer (1953): *Acta Un. int. Cancr.*, 9, 443.
Kennaway, E. L., and Kennaway, N. M. (1947): *Brit. J. Cancer*, 1, 260.
Kettle, E. H. (1932): *J. Path. Bact.*, 35, 395.
King, E. J., Clegg, J. W., and Rae, V. M. (1946): *Thorax*, 1, 188.
Knox, J. F. (1955): *Lancet*, I, 1275.
——, and Beattie, J. (1954): *A.M.A. Arch. industr. Hyg.*, 10, 23, 30.
Løken, A. C. (1950): *T. norske Lægeforen*, No. 11, 375.
Lynch, K. M. (1956): *Proc. Amer. Canc. Soc.*, 77.
Mastromatteo, E. (1955): *Brit. J. industr. Med.*, 12, 240.
Meiklejohn, A. (1956): 'Industrial Medicine and Hygiene', edited by E. R. A. Merewether, London, vol. 3.
Policard, A., and Collet, A. (1952): *Arch. industr. Hyg.*, 5, 527.
Public Health Reports, Washington (1952): No. 192.
Scott, T. S., and Williams, M. A. C. (1957): *Brit. J. industr. Med.*, 14, 150.
Turner, H. M., and Martin, W. J. (1949): *Brit. med J.*, II, 1148.
Weil, C. S., Smyth, H. F., and Nale, T. W. (1952): *Arch. industr. Hyg.*, 5, 535.
Werber, M. (1952): *Zbl. Arbeitsmed.*, 2, 179.
Wynn, H. (1951): *Postgrad. med. J.*, 25, 631.