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OCCUPATIONAL CARCINOGENESIS

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Not even the most sanguine would claim that the present state of knowledge on the fundamental cause or causes of non-occupational neoplastic disease is so far advanced that reasonable hope may be entertained of a curative or inhibitory chemotherapy or of a satisfactory preventive technique in the near future.

It is manifest that a great deal has been learnt in the last thirty years on the reaction of animal tissues and cells to a large number of synthetic chemical compounds and complex mixtures possessing carcinogenic properties. The imposing list of such compounds is rather a cause for depression than for hope, for the immense variety of structure of these materials seems almost to rule out any unitary hypothesis on how the effects are brought about. The chemical view of the etiology of cancer in man has naturally received great support from this work. Even the dilemma of the tumours induced in animals by virus does not present an insuperable barrier to the chemical view, for the time must come when the action of a virus will be expressible in terms of chemistry. It is the ancillary but vital character of a virus in the epidemiological field which might colour the picture, but the ultimate action on the cell must be of a chemical nature.

THEORIES OF CAUSATION

Whether it is a chemical compound as such or one produced by or incorporated in the structure of a virus, it is necessary for the carcinogenic agent to come into intimate contact with the cell which ultimately undergoes the change in character and rate of division which we call cancer. Various views are available as to what is the basic nature of such change, for example, that the enzymatic life of the cell is transformed; that the cell undergoes a type of mutation; that the normal processes of control or inhibition of growth are neutralized by carcinogens; that the cancerous transformation is really an adaptation of normal cells to adverse conditions created by the carcinogen; that the cancer cell arises from a slow breakdown of the activities of normal cells and not from a stimulus to its growth capacity, and no doubt many others. The common character of all such theories is that a point is reached in their exposition when experiment is left aside and imagination is allowed to enter.

The irreversible nature of the carcinogenic process which sometimes seems remarkable is perhaps not so surprising when the quite undisturbing irreversibility of tissue and organ differentiation from the primordial cell is borne in mind. The chemical nature of the so-called "organizers" which are apparently responsible for specific embryological differentiations seems well

established. There is probably a considerable specificity in the nature of organizers, bringing about definite effects. Such specificity does not, on the surface at any rate, appear to apply to carcinogens. Tumours can be induced experimentally in animals which are indistinguishable from tumours arising in man, both "spontaneously" and as a result of occupational absorption of the experimental carcinogen which is quite foreign to the metabolism of man.

EXPERIMENTAL EVIDENCE

The ultimate object in all cancer research is to prevent, inhibit or reverse the carcinogenic process. A great deal of experimental work has been done to attain this object in the case of experimental cancer. The skin cancer induced in mouse skin by the polycyclic hydrocarbons (e.g. 3:4-benzpyrene or 1,2,5,6-dibenzanthracene) and certain of their derivatives can be inhibited in different degrees by such widely differing substances as mustard gas and some of its derivatives, cantharidine, carbon dioxide snow, aliphatic aldehydes, and even strong sunlight. Even such unexpected compounds as naphthalene, anthracene and phenanthrene and bromobenzene were found to be inhibitory, and the fact that these compounds are excreted in animals in the form of mercapturic acid derivatives which arise from the condensation of a molecule of the compound and a molecule of the N-acetyl derivative of cysteine, led to speculation as to the importance in carcinogenesis of the deviation of sulphur from the normal metabolism of the skin cells. But even such anti-carcinogenic action in what must, compared with "spontaneous" cancer, be regarded as a relatively simple situation, is in no sense specific. Thus, certain skin-irritant compounds can act as co-carcinogens on mouse skin, but in appropriate dosage these can also act as anti-carcinogens, e.g. croton oil and croton resin; and the same applies to anti-carcinogens.

In all experimentation of this kind the inducer of the tumour and how it entered the body is known, the tissue affected is known, the nature of the tumour is known, and much of the relevant history of the animal is known. In human "spontaneous" tumours the nature of the tumour is, in general, known, the tissue affected is known, a little of the history of the animal is known, but of the inducer and how it entered, became active or was manufactured in the body, nothing is known.

In human occupational tumours a considerable amount is known about the inducer of the tumour as well as how it entered the body, in addition to the other elements referred to. It therefore follows that, just as in the experimental animal, the development of tumours can be prevented by not carrying out the experiment, so the occupational neoplasms need not develop if the "experiment" of exposing the worker to industrial carcinogens is not carried out.

SPONTANEOUS TUMOURS: PREDISPOSING FACTORS

Nothing is positively known, on the other hand, about how to prevent the "spontaneous" human tumours. Since tumours of this kind develop in

every class of human society, no absolute case can be made out for any obvious environmental factors, although statistical evidence may show a preponderance of certain forms of neoplasm in the poorer strata of society. It is probable that if a cross-section of society could be taken and wrapped in what might be called economic and physical cotton-wool, the incidence of tumours would in course of time be found to be quantitatively lower but qualitatively very similar to that found in normal conditions, i.e., there would be a cancer age-group, certain forms of tumours would be predominantly male or female in their sex incidence, and so on.

Genetic factors appear to enter in the appearance of "spontaneous" human tumours and there can be no doubt about them in certain animal strains. Attempts to demonstrate the weight of genetic character on the development of occupational tumours are not easy, in spite of the frequent presence of members of the same family tree in an industry with a carcinogenic hazard.

That *dietary factors* may enter as accessories in the etiology of human cancer has been considered in great detail but results have been inconclusive. Studies of records of American Insurance Companies led to the conclusion that there was a correlation between overweight and an increased liability to cancer. The same investigator, five years later, showed that both spontaneous and artificially induced tumours in mice can be delayed or even prevented when a carbohydrate-deficient diet was fed containing all the other recognized food constituents. Of course, such animals are stunted and there follows great endocrine atrophy. In this state the animals become refractory to the most active carcinogenic compounds. The recommendation by this investigator that diminished food intake should be practised as a prophylactic measure against cancer is perhaps a little naïve. When, as in the case of occupational tumours, the cause of the neoplastic process is known, no influence on the liability to develop the tumours which can be attributed to dietary habit has been discovered: such tumours develop in the well-nourished and in the relatively undernourished.

Age as a factor in the incidence of "spontaneous" tumours in man has for long been held to have a special significance, in spite of the apparent contradiction between the extreme vitality of a malignant process and the diminished vitality of the host body in which all passion appeared to be spent. Indeed, in some sense a cancer seems to be a process of local rejuvenation refusing to be bound by the general senescence. Age as a factor in occupational tumours is of secondary importance. Whilst it is true that occupational tumours often take many years to develop, the determinant as to the age at which they appear depends upon the age at which the tumour-inducing hazard was first met and how intensely the exposure continued.

CLINICAL AND PATHOLOGICAL FEATURES

However different the causes of occupational tumours may be from the unknown cause of "spontaneous" tumours, the clinical and pathological

features are more or less identical. This is the more evident in that the occupational tumour may appear many years after all demonstrable vestige of the carcinogenic hazard has long since disappeared. There can be no doubt that before the importance of occupational exposures was fully appreciated, tumours were seen in hospital which were in all respects identical and yet belonged in some cases (unknown to the surgeon or pathologist) to the occupational and in others to the non-occupational groups. This fundamental fact must be appreciated in order to realize fully the non-specific character of carcinogens. The manner in which the affected tissue reacts to the carcinogenic insult is non-discriminating so far as the latter is concerned. Thus, a bronchial carcinoma is the same whether it arises from the action of the mysterious "spontaneous" agent or from exposure to chromates; a carcinoma or papilloma of the bladder arising from exposure to certain aromatic amines is indistinguishable from the bladder tumours arising in everyday life; cancer of the lung is indistinguishable whether it arises from radium emanation or from the unknown spontaneous agents. Hence it will be apparent that no better prognosis can be given for occupational than for non-occupational tumours. An advantage lies with the occupational case inasmuch as, the hazard being known, appropriate protective measures can be taken and earlier diagnosis may be possible.

Although the tissue that reacts to potent carcinogenic agents does not discriminate between one or other of them, so far as the qualitative nature of the reaction is concerned, there must exist some difference as between individual tissues and between individual members of a species in the "mechanisms" of response to, or detoxication of, carcinogens. The same principle applies in occupational carcinogenesis. Thus, absorption of any of several aromatic amines over a period of years leads to tumours of only one organ, the bladder; great variation between individual members of a working team occurs, inasmuch as some develop tumours in a few years, others after many years, some after having left the industry altogether, and still others not at all.

Such individual variation is a commonplace in experimental work with animals bred with every precaution to approach genetic uniformity and used only at the same age, of the same sex, fed with the same diet, of the same weight, and so on. In spite of these precautions against variability of response to any given agent, toxic, carcinogenic, pharmacological, and the like, responses are obtained which require statistical treatment in the same way as a population of individuals. In other words, if a single individual is taken at random from the group of animals to be used for an experiment, it is not possible, however carefully uniformity has apparently been assured, to foretell with certainty what the response of the individual will be; we can only express the response as a probability. What lies at the root of this peculiar but universal individual variation nobody can say, but it clearly lends colour to the life of even a humble mouse or rat. In the case of man any other arrangement is unthinkable. If all men reacted in the same way,

whether psychologically or physically, to external forces, it would require only one severe epidemic to wipe out the species. It may be permitted to quote, in this connexion, a great French mathematical-physicist, Poincaré, who said: "C'est l'asymmetrie qui crée le phénomène", and to translate it freely thus: "Uniformity is death; to have life there must be variation".

A notable respect in which occupational and "spontaneous" tumours differ is that whereas in the latter it is as yet impossible to foretell when or where a tumour is likely to arise, in the former the clinical eye can be guided to the region in which tumours are likely to occur. Human mammary cancer has been shown sufficiently often to have familiar characters to render rational a look-out for its occurrence in sisters and close female relatives in the appropriate family. But it is rarely that a medical attendant inquires into the family history of a member of his panel *before* disease begins.

On the other hand, the medical observer in an industry involving a carcinogenic hazard knows or suspects where tumours will occur and directs his scrutiny to those parts. Thus, whereas in the manufacture of briquettes (patent fuel) attention will be directed to the incidence of skin tumours on the head and neck due to pitch; in the cotton industry with a hazard due to mineral oil the part to observe is the scrotum.

Accepting the general principle that the anticipation of the development of an occupational tumour permits of much earlier diagnosis, it is manifest that for any real value to attach to it, it must be possible to say that the disease thus diagnosed can be cured or the condition improved.

SELECTION OF WORKERS

Before proceeding to consider some aspects of occupational carcinogenesis more closely, a word must be said about the selection of workers for industries entailing a cancer hazard. Nothing is easier than to compose a pontifical statement on the medical requirements to be fulfilled before a worker is engaged to work in an industry in which sooner or later there is a danger of his developing a tumour in some region or other. But too much dogmatism in laying down criteria of employability is ill-advised.

The genetic factor.—A common demand is that there should be no history of cancer in the prospective employee's family. Indeed, in respect of one type of occupational tumour, I have made such a statement. But to what extent is there evidence that the liability to cancer in certain kinds of industry is increased by a family history of the disease? The answer must depend to a great extent upon one's own experience and presuppositions. Thus, I have observed the same occupational cancer develop in a father and a son, in two brothers, and in two or three members of the same line, all employed at different times in the same factory. This is a very different thing from saying that there is a family tendency unless a great deal more evidence is obtained, for each of these observations may have been due to chance. But it is undesirable to run the risk of a family build-up unless the

improvement of conditions of work is so great as to have reduced the hazard to vanishing point.

The age factor.—Another criterion often insisted upon is that the prospective employee should be a young, healthy adult. A formula of this kind is liable to be given as almost self-evident. Assuming that a considerable carcinogenic hazard still exists in a factory, the presumption in the formula is that a young, healthy man is less likely to develop an occupational tumour than a middle-aged or not completely fit person. We know of no evidence for such a presumption.

The determinants of the development of occupational tumours are *length and intensity of exposure* to the carcinogenic agent, and the individual power to detoxicate or inactivate the carcinogen. Consider the experience in this country in the case of pitch and tar epithelioma and in shale and mineral oil epithelioma of the skin. Of the former actual cases some 60 per cent. occur after 20 or less years of exposure, whereas of the latter only some 3 per cent. occur after 20 years or less of exposure, and some 64 per cent. occur after 55 years or less of exposure. Thus if a young man, of say twenty years of age, enters operations involving contact with pitch and tar or tar products and if he develops a tumour, he has a 60 per cent. chance of doing so before he is forty. If, on the other hand, he undertakes work involving contact with shale or mineral oil, and if he develops a tumour, the corresponding chance is only 3 per cent. Thus, it does not seem unreasonable to say that it is less fair to put a young man on to pitch and tar work than on to shale and mineral oil work. This does not mean that we regard middle-aged men as something to be sacrificed. Far from it. It means that a middle-aged man may run most of his life's course before he gets a tumour at all. Latency of the occupational tumour in ordinary industrial conditions should always be fully understood before any statement is made on the desirable age for new starters in the hazardous operations.

The health factor.—It will be clear that "health" in a prospective employee must be interpreted in the light of the hazard into which he is about to enter. In the first place, if the carcinogenic hazard is one affecting the skin, it is apparent that skin diseases (e.g. warts) or sensitivities should preclude from entry; if the hazard is one involving a carcinogenic dust, it is clear that any condition which induces any measure of dyspnœa must be precluded, e.g. asthma, bronchitis, obesity, cardiac conditions, even when these are not sufficiently troublesome to prejudice ordinary working capacity; if the hazard involves a carcinogenic effect on the urinary tract, it is obvious that any degree of urinary dysfunction or infection must be precluded; if we may include cleanliness as an adjunct of health, then a dirty worker should never be permitted to continue working in a dangerous toxic process; finally, since the health of a man may have much to do with his habits, it is essential to prohibit nail-biters, tobacco-chewers, snuff-takers, surreptitious suckers of sweets and partakers of snacks.

Intelligence in the worker.—It is best to employ intelligent workers on

processes which involve the subtle and furtive hazard of an industrial carcinogen. The overt manifestations of acutely toxic effects will more or less readily impress themselves on the mind of the least endowed workman, especially if there is danger of what is called "gassing" or if there is evidence of irritant fume or dust. When dealing with liquids or non-irritant dusts or solids, it is much more difficult to impress the average workman. Now, a carcinogenic hazard must involve an employer in the moral obligation to inform his workers minutely on what is involved. The reaction of a worker to such information depends upon his intelligence, for, provided the employer goes to the limit in precaution and the informed workman exerts all his faculties in careful operation and good housekeeping, there is good and reasonable ground for confidence in his safety. But it will not be overlooked that we have used the phrase, "provided the employer goes to the limit". Mere adherence to statutory requirements in the Factories Act, Regulations and Orders is not enough; these are minimum, not optimum.

CARCINOGENIC AGENTS

I proceed now to consider occupational carcinogenesis more especially in relation to the industries or occupations in which it is observed.

If we ask the question, what are the occupational carcinogens, the answer must satisfy criteria that the substances indicated are carcinogens experimentally and that they produce cancer in man in industry. To demonstrate unequivocally that a substance is a carcinogen we must have recourse to animal experiment. Thus, although the relation between coal tar and occupational skin tumours was discovered as long ago as 1875, there was a hiatus of forty years before Japanese investigators produced definite malignant epitheliomas by applying coal tar to the ears of rabbits. Since those days a host of compounds has been tested on animals, and unless a material suspected of producing occupational tumours yields positive results in animals of one species or another we cannot say more than that it is suspect. This is the position at the present time with chromates; evidence in favour of their producing occupational cancer of the lung is strong, but they have never been shown to do so experimentally.

It must be emphasized, however, that we are far from being able to say that because a particular substance is a carcinogen to animals it is also a carcinogen to man, and it would be dangerous to conclude that because it has not been shown to be a carcinogen in animals that it is therefore not a carcinogen to man. The demonstration of carcinogenic properties in animals engenders a reasonable fear that the material involved may also be carcinogenic to man. But the demonstration of carcinogenicity in man may never be possible. Thus, the notorious dye "butter yellow", *p*-dimethylaminoazobenzene, is indubitably a liver carcinogen to a variety of species and has long been forbidden as a food colour, but no evidence that it has ever had carcinogenic effects in man has been, or ever will be, obtained. Many azo compounds have been shown to possess carcinogenic properties in animals, but

no reasonable evidence has ever been obtained that men in a dye factory handling only uncontaminated azo compounds, including azo dyestuffs, are especially liable to develop tumours. On the other hand, it has never been shown that the dye intermediate, benzidine, is a carcinogen to animals, but there is no reasonable doubt that it is a carcinogen to man.

It has recently been pointed out by Salter (1948) that "despite a wealth of data indicating carcinogenesis in man from crude mixtures, only three *unadulterated* agents have thus far been *proved* carcinogenic for man. These are (a) radiation, (b) beta-naphthylamine and (c) arsenic".

RADIATION

The evidence for skin carcinoma in white workers much exposed to sunlight in tropical or semi-tropical lands is widely accepted. The effect of intense ultra-violet light on the much thinner skin of rodents is to produce sarcoma or mixed tumours, the difference probably being that whereas the relatively thick horny layer of man absorbs the ultra-violet radiation, in the rodent the latter penetrates to the subepithelial layers and acts on the connective tissue there located.

X-rays.—Statistics of the incidence of cancer and related conditions (e.g. leukæmia) among radiologists, X-ray tube makers and technicians show a definite occupational hazard for these workers. The direct demonstration of the development of tumours of the skin from exposure to X-rays has been made during the treatment of certain skin conditions with this agent, e.g. hypertrichosis of the face, psoriasis, lupus. The final confirmation of the carcinogenic action of X-rays was made by exposing the skin of rodents for many months to this action; spindle-cell sarcomas developed.

Radioactive substances.—As long ago as 1879, it was shown that the rapidly wasting disease with manifest pulmonary damage which had for centuries been observed in miners in the Erz Mountains (between Saxony and Bohemia), was due to a circumscribed lung tumour. In subsequent years there were various theories of the ultimate cause of the condition (e.g. uranium, cobalt, arsenic), but the measurement of the radioactivity in these mines in the early 1920's left no doubt that the miners were inhaling very large amounts of radioactive material, whether as actual radium compounds or as radon gas. An interesting feature of these tumours was, and still is, that the lung tumours may not appear until many years after the miners have left the mines altogether. This latency is so frequent an accompaniment of occupational tumours as to be almost a specific character of them.

The alarming recognition years ago, both in this country and in the United States, that persons engaged in the application of radioactive compounds to surfaces and in the introduction of such compounds into glass tubing (luminizing operations) were liable to develop severe anæmia of aplastic type and sarcoma of bone, led to the important Luminizing Order of 1942. This order is meticulously designed to prevent the ingestion and

inhalation of radioactive material during work, and the contamination of skin, hair and clothing and items in the environment with it.

The final confirmation experimentally of the carcinogenic effects of radioactive materials has been produced in the years since the end of the 1939-45 war, as a result of work with plutonium (Pu_{239}) and fission products of uranium (U_{235}). Thus, 1μg. of Pu_{239} injected into mice will produce sarcoma at the site of injection; deep penetrating radiations (γ) lead to blood disease, and the less penetrating (α) to cancer of the skin in all animals exposed.

Thus the proof of the carcinogenicity of these various kinds of radiation is complete. It is fortunate (or unfortunate, according to the point of view) that the detection of dangerous conditions of work or dangerous levels of absorption is carried out by highly precise physical methods (e.g. calibrated photographic films, Geiger-Müller counters), and hence it should be possible to eliminate serious hazard. Observation of the manner in which safety measures are installed and operated in handling compounds of radium and radioactive isotopes leaves little doubt that, except in the case of accident, the safe tolerated dose of radiation (0.3r-0.5r per 5-day week) will not be exceeded.

AROMATIC AMINO COMPOUNDS

Salter's inclusion of β-*naphthylamine* as a fully demonstrated carcinogen rests upon increasing knowledge of the remarkable incidence of bladder tumours among workers engaged in the manufacture of dye intermediates, i.e. aromatic amino compounds from which, with other compounds of greater or less complexity, the final dyestuff product is built up. Whereas the original description of a suspiciously high incidence of bladder tumours in this industry goes back more than fifty years, the impress of the disease upon countries in which a big-scale dyestuffs industry was developed relatively late became manifest only in the last twenty years or so (e.g. U.S.A., Britain and even more recently France).

Several aromatic amines were for a good many years suspected as the carcinogens responsible, e.g. aniline, benzidine, α-naphthylamine and β-naphthylamine. Only in the last ten or twelve years has experimental evidence been obtained in dogs that one of these compounds, β-naphthylamine, is indeed a potent carcinogen.

Although several workers, two in America and one in Britain, have obtained tumours in dogs or bitches with large doses of this compound administered for several years, the report of Gehrmann, Foulger and Fleming (1949) has shown that 300 mg. of β-naphthylamine, administered daily for five days a week until fifty doses had been given and produced in dogs (several groups of three or four) many signs (urinary and cystoscopic) premonitory of the development of tumours. The minimum time for this effect was fifty days. Cessation of administration of the compound was followed by return of the bladder to what seemed a normal condition in a few weeks. But carcinoma was found in one bladder at autopsy six-and-a-half years later, and pre-neoplastic changes in another. This latter observation is the counterpart of what happens to workers who after some years of exposure in the industry may leave it apparently unscathed, and develop a bladder tumour many years later. For a sub-

stance to produce this effect after only fifty days of administration qualifies it to be included among the most potent carcinogens.

Gehrmann *et al.* (1949) made the further observation, by exactly similar experiments on bitches, that benzidine (171 mg. daily for 5 years), pure α-naphthylamine (301 mg. daily for 4½ years) (α-naphthylamine as manufactured in this country contains 3-5 per cent. β-naphthylamine and has been known for many years to produce tumours in the bladder); aniline (300 mg. daily for 2 years), tolidine, 230 mg. daily for 3 years, and dianisidine, 291 mg. daily for 3½ years, produced no tumours in any of the twenty-four dogs used for these compounds.

Similar experiments in this country have also failed to show that aniline and benzidine are carcinogens in animals.

Occupational *cancer of the bladder* is a notifiable and scheduled industrial disease in most countries where the problem arises (e.g. U.S.A., Germany, Switzerland, France, Italy), but not in Britain. The disease is especially interesting for its almost exclusive attack on the bladder; very rarely a primary tumour of the renal pelvis or ureter is seen. It may start as a non-malignant papilloma or as a carcinoma, very often in the trigone and perhaps most frequently in the vicinity of the ureteric orifices. The dilemma is obvious if the condition is to be described as an industrial disease in the manner employed in this country; that is, with specification of the process, not merely the industry.

ARSENIC COMPOUNDS

Cancer of the skin among workers exposed to the hazard of absorption of arsenic compounds has been known for more than a hundred years. Ullman, in his well-known "Handbook of Skin and Venereal Diseases", gives a collection of 72 cases of cancer attributed to arsenic, most of which were due to long treatment with arsenical preparations. Sir Thomas Legge in this country, nearly fifty years ago, associated the familiar skin changes induced by arsenic compounds, pigmentation and hyperkeratosis, with irritation of the upper air passages and perforation of the nasal septum when the hazard was an arsenical dust.

Cases of *skin cancer* have been described among a great variety of workmen in contact with arsenical compounds, for example, men in arsenic mines, in tin foundries, in preparing or using arsenical sheep-dip, in copper smelting, in glass-factories, and in the handling and use of arsenical pesticides.

Intermittent reports appear of *lung cancer* in workers handling arsenical compounds. Thus, in his 1943 Annual Report, the Senior Medical Inspector of Factories stated that "The etiological relationship between malignant disease of the lungs and exposure to arsenical dusts is a matter of importance . . . The number of cases which has come to our notice is, however, few . . ." Between 1939 and 1943 four such cases were notified, all in workers with sheep-dip containing sodium arsenite. Currie, a Medical Inspector of Factories, in a recent article (1947), refers to a fatal case of a columnar-celled adenocarcinoma of the lung in a worker who had been exposed to arsenical

dust for forty-three years, and to one of skin cancer complicated by lung cancer in a worker in arsenical insecticides.

The clinical evidence in favour of the carcinogenic action of arsenic is undeniably strong, but the experimental evidence with animals is surprisingly slight.

Leitch and Kennaway's frequently quoted experiments were on painting mouse-skin 3 times daily with a 1.8 per cent. alcoholic solution of potassium arsenite. This highly toxic solution had to be replaced by a 0.12 per cent. solution. After 86 days, the experiment yielded one animal out of 100 with a squamous-celled epithelioma and Leitch's own later experiments yielded no tumours at all. There were many fatalities. Hyperkeratosis and hyperpigmentation produced by arsenic have been demonstrated by other investigators.

Reviewing the evidence, it seems reasonable to agree with Salter (1948) that radiation, β-naphthylamine and arsenic can be identified as carcinogenic agents in man, and that there is varying weight of evidence that they are also carcinogenic in animals.

OTHER OCCUPATIONAL CARCINOGENS

We must now consider whether or not in other cases of known or alleged occupational carcinogens an identifiable cause can be held to be responsible.

When in 1915, Yamagawa and Ichikawa produced skin carcinoma on the external ear of rabbits by repeated applications of *coal tar*, and Passey in 1922 induced malignant growth on the skin of mice with ether extracts of soot, the stage seemed to be set to identify the active compounds in these complex mixtures. From this period began the remarkable work of Kennaway and his school: the demonstration by Kennaway of the carcinogenic properties of tars obtained by pyrolysis from mineral oil, coal, skin, yeast, hair, and by subjecting relatively simple saturated and unsaturated hydrocarbons to heat in the presence of hydrogen; the study of the characteristic fluorescence spectra of carcinogenic tars and oils and the later recognition that the polycyclic hydrocarbon 1:2-benzanthracene possessed a fluorescence spectrum of a similar character; the syntheses of homologues of benzanthracene leading later to a great increase of synthetic carcinogens; the isolation from coal tar pitch of a pure hydrocarbon which showed the characteristic spectrum and was a potent carcinogen, and its later identification as 3:4-benzpyrene; and the relatively recent recovery of about 75 mg. of pure benzpyrene from 10 g. of crude tar distillate. It may safely be supposed that the actual benzpyrene content of tar is very much more than this having regard to inevitable losses in purification.

The chain of evidence seems complete that 3:4-benzpyrene is the constituent in tar responsible for human cancer *but there is no direct evidence that this is so.* No doubt evidence will appear that the omnipresent town-soot contains similar or identical carcinogenic hydrocarbons, but its reference to the incidence of, say, cancer of the lung (which is certainly on the increase) will be hypothetical until the relation between animal carcinogens and human carcinogens is established.

Asbestos.—As long ago as 1938 the suspicion arose that asbestos workers might be more than normally prone to lung cancer.

Nordmann (1938) analysed six cases of lung cancer and showed that the range of exposure periods was 7 to 21 years, and the range of intervals between entering the industry and death was 15 to 21 years. The malignant disease in some cases occurred years after leaving the industry. Half of these cases were comparatively young, 35 to 41 years of age at death. In one remarkable case a seventy-one year old woman had worked in asbestos for only 19 months. Later in the same year he referred (1938) to a further seven cases of associated asbestosis and lung cancer, including Gloyne's finding of six cases of carcinoma of the lung in 50 autopsied cases of asbestosis.

In the 1947 Annual Report of the Chief Inspector of Factories, the Senior Medical Inspector tabulated the age incidence among 235 deaths caused by asbestosis: in 13.2 per cent. of these cancer of the lung was present, and it is especially important to note that 4.8 per cent. of the age-group twenty-five to thirty-four, and 5.6 per cent. of the age-group thirty-five to forty-four had this condition. It will be seen that the over-all figure is closely in agreement with Gloyne's findings.

The establishment of the well-known diffuse pulmonary fibrosis induced by exposure to asbestos fibres is usually regarded as due to mechanical action, and some evidence of this is presented by finely grinding the asbestos to particles less than 2μ in length, whereby the fibrosis effect is eliminated in animal experiment. The reverse would be the case with silica. But when so much has been said, it still remains a puzzle why cancer should favour the asbestosis lung and not the silicotic lung. Silica is held to act by local solution and chemical action: asbestos (a hydrated magnesium silicate) is held to act as an irritant in virtue of its physical form. The next step, to bring cancer in the asbestosis lung into line with a chemical theory of cancer, has not been taken.

Nickel carbonyl.—It has been known for a long time that workers in nickel refineries develop remarkable tumours of the ethmoid region of the nose and bronchogenic carcinoma of the lung. Like so many other occupational cancers it may occur many years after exposure to the carcinogen has ceased.

Amor's (1939) interesting analysis of ten cases of cancer of the ethmoids and four of lung cancer shows that the average period from first exposure to the hazard (*vide infra*) until death was some 17 years (range 11-28) for cancer of the ethmoids and 20 years (range 9-27) for cancer of the lung. In this series the nasal tumours attacked the middle turbinates and the ethmoidal air cells. These were all carcinomas of various kinds, squamous, columnar-celled and undifferentiated.

I introduce nickel into this short discussion mainly because its association with the problems of occupational cancer is a very good example of a cryptic cause.

In the separation of nickel from its ores the problem before the technologist is to fractionate the ore in such a way that not only nickel but several other valuable metals always found in association with nickel will also be recovered. It is the manner in which this fractionation is carried out which determines whether or not the process will include the hazard of cancer. Nickel is usually extracted in this country from Canadian ore and the latter must undergo a considerable number of processes before

it is rendered suitable in nickel content for the process of electrolysis or the Mond procedure (formation of nickel carbonyl and its subsequent decomposition by heat). The original ore consists of a number of metallic sulphides (Cu, Fe ,and small amounts of Co and rare metals) deposited in rock. By processes of flotation the rock can be deposited from the ore and various levels separated off which permit a top layer rich in copper and nickel. By calcination of this, SO_2 is liberated and converted to sulphuric acid and acid sodium sulphate. Further treatment in a reverberatory furnace and then in a Bessemer converter permits of a final product ready for refining which may contain up to 80 per cent. (Ni + Cu).

The modern first process of refining is to heat this product with $NaHSO_4$ and coke, which yields a molten product consisting of two layers, an upper solution of CuS in Na_2S and a lower of nickel sulphide. This process is repeated to produce a better product. But the copper can also be removed by treatment with sulphuric acid and recovery as copper sulphate, and this was the method used in the British factories. In either case the residues after removing copper in one form or another consist mainly of metallic sulphides and must undergo drying, grinding and calcination to produce metallic oxides, all very dusty operations. A long time had clearly to elapse before the danger could be realized. Having regard to the nature of the disease it could hardly fail to be realized that a dust hazard was involved.

In the subsequent processes of refinement, whether by electrolysis as used in Canada or the carbonyl process as used in Britain, the hazard is of a quite different kind. The latter process, which was regarded with suspicion by some, involves the reduction of the oxide by means of water gas (60 per cent. hydrogen and 36 per cent. carbon monoxide) kept at about 350° C. by hot air circulation. Now although both hydrogen and carbon monoxide are reducing agents, at the low temperature at which the reaction is run nearly all the reduction is due to hydrogen. The effect of this is to use up the hydrogen and enrich the emergent gases in carbon monoxide. The crude metal is now made to meet the CO-rich water gas; the nickel combines with the CO and forms a very volatile compound $Ni(CO)_4$—nickel carbonyl—which is carried over as gas to be decomposed at 180° C. on heated nickel pellets, on which the liberated nickel is deposited; the liberated CO being re-used to form more carbonyl. The further processes of extraction of rare metals and cobalt need not concern us here.

The point was to discover the carcinogen in this complicated process once it had been made clear that both ethmoid and lung cancer were prevalent. Let it be said at once that neither nickel nor nickel oxide nor nickel salts could be shown to be carcinogenic in various experiments. Further (as stated by Amor) the incidence of malignant disease among workers in exactly similar conditions of process and work in Canada was not increased, *but the Canadian process did not include the use of sulphuric acid for the separation of copper*. Nickel carbonyl itself is a highly toxic product and when inhaled it is decomposed with the deposition of nickel in the lung and liberation of CO. This evidently constituted the rationale of the testing of finely divided metallic nickel for carcinogenic properties.

Nickel carbonyl poisoning in man leads to pulmonary œdema and cerebral and pulmonary hæmorrhages; in animals the same effects can be demonstrated as well as hæmorrhages in the bronchi and trachea and nasopharynx, and sometimes in the adrenals. These facts, combined with the freedom from malignant disease of men engaged in the manufacture of nickel carbonyl, and the additional absence of evidence of ethmoid or lung cancers among men getting the ore or carrying out the pre-refining processes, left the extraction of the copper from the matte to be studied.

The difference between the Canadian and Mond processes was the use of

sulphuric acid for the extraction of copper and in this sulphuric acid a high content of *arsenic* was eventually found. In the period relevant to the present discussion an ordinary commercial sulphuric acid of specific gravity 1.7 might contain 3.18 g. As_2O_3, 2.56 g. As_2O_5 per litre (*Chemical Trade Journal*, 1906), and so would readily form insoluble arsenical compounds of copper (including arsenides). Removal of the copper sulphate would leave the residual nickel and other metals still contaminated with Cu-As compounds. On drying, grinding and calcining, enormous amounts of arsenic-rich dust would be evolved and, as proper precautions were certainly not taken forty or more years ago, the stage was set to produce the slowly developing arsenical cancers. In spite of vast improvements in process and safety, cases still arise in this country among men who had been exposed to the old process and to which their condition must be attributed. The attribution of the tumours to arsenic is, of course, an inference, but one based upon almost incontrovertible evidence.

CONCLUSION

It is not possible in a short article to enter adequately into the many other inducers of occupational tumours, e.g. chromate, beryllium, and the industrial materials which produce blood diseases simulating neoplastic disease, e.g. benzene. Research continues apace in academic and industrial laboratories to cast more light on the nature of more obscure occupational conditions.

As the civilized world becomes more and more dependent upon the products of industry, and the persistence of chemists brings to light more and more complex compounds with desirable or often undesirable properties, it is the business of experimentalists in the physiological, pathological and biochemical fields to elucidate their effects on man and try to protect mankind from its own ingenuity.

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