OCCUPATIONAL CANCER*

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PART 1

The expression "occupational cancer" in reality refers only to a predisposition to the disease, caused by the action of a group of commodities used in certain trades and occupations. The substances in question do not directly cause cancer, but affect the tissues in such a way (usually by giving rise to cell-proliferation of an adventitious type) that the site is rendered specifically prone to malignant invasion. It is well known that soot is one of these commodities, and there is considerable evidence that tobacco-smoke helps in causing the incidence of epithelioma in the throat and larynx. It has generally been considered that this predisposition is due merely to mechanical "irritation" of the tissues, and therefore the subject has not hitherto received much if any systematic investigation, for it is common knowledge that chronic mechanical injury in certain tissues during senescence is liable to predispose to malignant invasion; but during the recent government enquiry into pitch cancer at the briquette works in South Wales some new clinical facts have been found out, which make it appear that some definite, if not specific, chemical rather than mechanical action is concerned in the causation of industrial cancer. 2 This has led to the investigation of other commodities the use of which also gives rise to cancer under certain conditions; and when all of them are examined collectively, there seems to be considerable

* The author has not read the proof of this article.
1 Late Director of the John Howard McFadden Research Fund.
2 The writer was called upon to give evidence at this enquiry, and it was in connection with it that the following investigations and experiments were made.

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evidence, both circumstantial and experimental, to show an association between certain chemical products of death and putrefaction contained in or produced by the commodities themselves and the onset of the disease.

As this evidence is clearly of value in the investigation of the general etiology of cancer, the several commodities will first be discussed seriatim, describing the sources and general properties of each substance, the clinical manner in which the disease is brought about, and their power of causing chemical versus mechanical "irritation." Later on the property of producing "smarting of the skin," a chronic dermatitis which is possibly in some instances the initial lesion, and which is an important industrial complaint in some of the trades, will be described. In the description of the commodities references will be given to the description of other commodities, so that comparisons can be made on the one hand as to the incidence of cancer and on the other as to the amount of mechanical injury caused.

It is convenient to take first the coal-tar derivatives and in the order in which they are produced commercially; but this order is inverse to the amount of disease to which the said commodities give rise.

COAL

Coal may be described as a residue of prolonged compression of vegetable matter which has undergone death and decomposition. Coal-miners, heavers, stokers, etc., become covered with coal-dust during their occupations, and yet, in remarkable contrast to its more concentrated products such as tar, pitch, and soot, coal does not give rise to warts and epithelioma. Occasionally a case is reported from one of the mines, but the incidence is rare. In the navy the writer never saw a case among the stokers, and the disease is not specially remarked upon by authorities on miners’ diseases.

Mechanical injury. Coal-dust is hard and gritty, and, if it is rubbed on the skin, the fragments are so sharp that they may cause mechanical injury almost amounting to laceration of the epidermis. But coal-dust can be readily washed off the skin.
At the gasworks coal is distilled for the production of gas; at the blast-furnaces it is used as fuel. Bituminous coal is mostly used in England at the gasworks and coke-ovens; for reasons which need not be mentioned here, the harder Scotch coal is mostly used at the blast-furnaces. In both these industries tar is produced as a by-product, and the varieties are generally known as gas-tar and blast-furnace-tar respectively.

**TAR**

Tar may be described as concentrated coal. It is the residue after the first stage in the distillation of coal. By far the greater quantity of it is produced at the gasworks and coke-ovens. Gas-tar varies considerably in its reaction and viscosity according to the temperature of its distillation and to the type of coal from which it is made. Chemically, it contains a large number of substances, some of which will be described later. Blast-furnace tar is very similar except that it is made from a different coal and that it comes over at a lower temperature.

Gas-tar causes warts and epithelioma on the hands and arms of the workmen who handle it, although the incidence is not so great as that caused by pitch or soot (see later). The action of tar is similar to that of crude paraffin, which will also be detailed later. Butlin quoted this action, as described by both Volkmann and Ogston, thus:

Substantially, the effects of the liquid tar and paraffin on the skin of those engaged in the manufacture and whose bodies are actually exposed to them, consisted in eruptions of an acute and chronic character. The acute forms sometimes passed off, and were so completely recovered from, that they scarcely left any trace behind them, but they passed on in many of the people to become chronic. In the acute form the hair follicles and sebaceous glands were chiefly affected, often with the production of an eruption of bright red nodules closely approx-

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4 The word "concentrated" is a convenient one to use in this connection as will be seen later, but it should be remembered that, in each stage of the carbonisation of coal and its derivatives, certain fractions are removed; but as the disease caused by each stage is more pronounced, the fractions removed evidently do not concern us.
imate to each other, and usually largest and most numerous on the wrist . . . . the dorsal aspects of the parts being most severely affected and the palms of the hands and soles of the feet enjoying a complete immunity. The red nodules correspond with the hair follicles. With the diminution and disappearance of the red eruption, the hair follicle remained enlarged, its mouth gaping and occupied by a little mass of epithelium and dirt, so that the black points were visible over the surface of the affected skin. The only difference in the descriptions of Ogston and Volkmann is that the former speaks of the hair follicles, the latter of the sebaceous glands, as the structures affected and the seat of the black points. In the chronic condition the skin between the hair follicles or sebaceous glands was also altered, it became thickened, dry and stiff, chiefly by increase in the thickness and alterations in the quality of the epidermis. Volkmann describes, in addition (probably because his observations extended over a longer period and were made on a larger number of individuals), little knots of epidermis, tiny horns, and flat, dirty brown scales and crusts. He found that the infiltrations on the skin were most frequent on the forearms and scrotum, where particularly they were prone to become moist and offensive.

It is the chronic condition that is liable to become malignant. Unfortunately there is no accurate return of the number of cases at the tar works, for these industries have not yet been scheduled as "dangerous trades," but from enquiries from the tar-distillers, cases of malignant invasion of the warty skin are not uncommon.

Blast-furnace tar, on the other hand, seems to be harmless.

Mechanical injury. There is an absence of fine particles or grit from tar, which is a viscous liquid at ordinary temperatures. In the strict sense of the term, therefore, it can hardly be accused of causing mechanical irritation, but when it dries on the skin, especially after vigorous washing, a little mechanical injury may be caused before it can be entirely removed from the pores.

Both gas-tar and the blast-furnace variety are consigned to the tar-distillers, who, by further carbonisation, obtain various commodities from it, such as ammoniacal liquor (sulphate of ammonia for manure), naphthas, creosotes, phenols, anthracene oils, and many others.
The residue is the black bitumen, which sets on cooling, known as gas-tar pitch and blast-furnace pitch respectively. Four-fifths of the pitch made is consigned to the briquette works.

**PITCH**

Pitch may be described as concentrated tar. Gas-tar pitch causes the disease known as pitch warts, which is fairly frequently followed by pitch cancer. The common site, as in the case of soot, is in the scrotum, but the warts also appear frequently on the face, neck, and lip; next to the scrotum, the lip is the commonest site for malignant invasion of the pitch wart. From time to time opinions are advanced that pitch cancer is not true cancer; but they can be disposed of by the fact that the disease is identical with chimney-sweeps' cancer, and has within the last year to the writer's knowledge caused at least two deaths in Swansea alone. It is true that the warts are not malignant at first, and there is evidence to show that they do not become malignant, in a manner similar to the case of tar, until ulceration has occurred, leaving an open sore at the base; but once they become malignant and remain untreated, the disease runs its usual course with metastasis and death, although, as the lesions involve the skin, the mortality is not very high owing to early detection and the facility for complete removal.

At the briquette works, pitch is ground into a fine powder and mixed with small coals, the mixture being dampened by steam and compressed into the blocks which constitute the "patent fuel." The pitch grinders suffer most, although there are some cases among the men who handle the briquettes. Out of 246 men examined by Dr. Legge, H. M. Inspector of Factories, 51 suffered from pitch warts and 28 showed signs of old ones. It is probable, as Mr. Commissioner Lush (1) has pointed out, that the incidence is higher than this, as the numbers examined included men other than the pitch grinders. In the writer's experience at the works, the incidence of pitch warts among the grinders is practically universal except in the cases of boys or young men.

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*1914, since then the disease has frequently occurred.*
It is remarkable how pitch warts become more common in the men as age advances, a point brought to light at one of the Home Office conferences with the briquette trade, and apparently in harmony with the etiology of tumors in general. The actual clinical condition cannot be better described than by the following quotation from Dr. Legge's Report (2), in which it is pointed out that the men engaged in the manufacture of briquettes are liable to suffer from warty growths, which ulcerate and occasionally become the seat of epitheliomatous cancer. The growths may occur on any part of the body, and are common on the face, hands, and scrotum. [The region where the collar rubs is a very common site.—H. C. R.] They commence as small nodules in the skin and almost immediately begin to break down, forming an ulcer covered by a crust, which gives the characteristic appearance to the so-called wart. The underlying ulcer almost invariably heals up, leaving a small scar when the crust has fallen off. We believe this to be the normal course, although witnesses regard the scar as the result of the primitive methods of treatment adopted by the workers. When they take on an epitheliomatous character the situation is almost invariably on the scrotum. The disease then follows the usual course, involving neighboring organs and tissues and can only be arrested by free excision. Epithelioma is the least malignant form of cancer, and on removal is not usually followed by recurrence. We saw men still at their ordinary work and in good health, on whom such operations had been performed several years previously. The amount of incapacity caused by the condition, whether in its benign or malignant manifestation, need not be great. There was general concensus of opinion that the cancerous conditions could be prevented by scrupulous cleanliness, but we satisfied ourselves that occasionally it may develop in those who have paid all reasonable attention in this respect.⁶

Blast-furnace pitch does not appear to cause either warts or cancer (1), (2). The difference is a most important one; and the government, in imposing regulations (1) to deal with pitch cancer, specifically exempted those factories in which only blast-furnace pitch is used. Yet the two forms of pitch are

⁶ The italics are mine—H. C. R.
practically identical except that the blast-furnace variety is made from tar which comes over at a lower temperature, and which is mostly made from the less bituminous Scottish coal.

Mechanical injury. Both forms of pitch are gritty, but less so than coal and more so than soot. At the hot temperatures of the briquette factories, ordinary pitch softens slightly on the men's skins, when it is sometimes difficult to remove; blast-furnace pitch, however, does not so easily soften.

Soot

This substance, which may be described as concentrated pitch, is the best known cause of industrial cancer. The mortality from it among chimney sweeps is twice what it is among occupied males generally. The mortality in 1900–1902 was 133 as compared with 63 among occupied males at the same age. "This excessive prevalence is certainly due to the nature of the trade, the soot setting up an irritation of the skin similar to that produced by pitch or tar and with similar results." (1)

The form of soot that gives rise to this disease is that produced by the carbonisation of coal; and more soot is set free by burning bituminous coal than by the use of the harder varieties, such as anthracite. Soot, however, is not pure carbon but also contains tar and tar oils with a certain amount of varying degrees of pitch. It is not gritty as a rule, but of a soft floury nature due to the tar oils, as can be readily demonstrated by placing some on blotting paper, when the oils will produce a greasy exudation. Owing to this oily nature, soot can only with difficulty be removed from the pores of the skin; but although the sweeps' bodies are covered with it from head to foot, like pitch, it causes the disease practically on the scrotum only—preceeded, as usual, by warts. This is a remarkable fact, but at the same time it should be remembered that with this class of workmen,

6 "There is 'sut' and 'sut,'" an expression frequently heard at tar and briquette works. Soot is the cause of chimney sweeps' cancer and is collected from domestic chimneys. "Sut" is practically clinker, consisting of carbon and earthy salts, like the smoke-box ashes produced in locomotive flues. High temperature and pressure furnaces produce the latter, which is harmless.
who rarely have baths, the scrotum is the dirtiest part of the body, and is constantly subjected to rubbing from dirty corduroy trousers. Moreover it is a part where sweating is profuse.

Mechanical injury. The absence of grit is an important point, because the floury soot differs in this respect very materially from coal-dust, which does not cause cancer at all, yet which will cause mechanical injury amounting to laceration.

We may now sum up the foregoing commodities to show the relative amount of mechanical irritation caused by each, comparing that with the amount of cancer caused by each.

<table>
<thead>
<tr>
<th>MECHANICAL INJURY</th>
<th>COMMODITY</th>
<th>CANCER INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greatest</td>
<td>Coal-dust</td>
<td>Nil</td>
</tr>
<tr>
<td>Considerable</td>
<td>Blast-furnace pitch</td>
<td>Nil</td>
</tr>
<tr>
<td>Only little, as it softens</td>
<td>Gas-tar pitch</td>
<td>Considerable</td>
</tr>
<tr>
<td>Practically nil, a liquid</td>
<td>Tar</td>
<td>Several cases, but less than pitch</td>
</tr>
<tr>
<td>Nil</td>
<td>Soot</td>
<td>Greatest incidence of all</td>
</tr>
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</table>

It seems clear from this clinical evidence that pitch warts and epithelioma in the coal-tar industries are not due merely to mechanical irritation, for the more the irritation the less the disease.

Since the predisposition is not due to mechanical injury, it is obvious that it must be due to chemical injury, which is borne out by the fact that it is the most concentrated form of coal, namely soot, which causes the most disease, the incidence among the intermediate trades rising in exact ratio with the concentration; thus, coal causes no warts or cancer, tar causes some cases, pitch causes many more, and soot causes a double mortality. The gradual concentration of the coal, therefore, also apparently concentrates at each stage of the distillation some substance which seems to be the predisposing cause of cancer in all these industries.

That some chemical factor is concerned is also evinced by the harmlessness of blast-furnace tar and pitch. These substances cause more mechanical injury than their gasworks prototypes,
and yet they have no cancer-producing action whatever. But the blast-furnace tar is produced at a lower temperature and from different coal, which makes it all the more probable that the mischievous chemical substance is less effective or absent from this commodity.

ANTHRACENE FRACTION OF TAR

There is a theory at the works that the mischievous substance is contained in the anthracene fraction of tar, because of recent years it has not paid, as formerly, to remove this fraction for the manufacture of dyes, and the leaving of it in the pitch coincides with the increase of the disease in the last decade or two.

NAPHTHALENE

It is also clear that the products of the lighter fractions are not to blame, because those who make boot-blacking and other "blacks" do not suffer. Boot-blacking is made by the carbonisation of naphthalene (isolated from a tar fraction lighter than the anthracene fraction) which is converted into a "soot" by burning on hot plates. The workmen in this industry become covered with this "soot," but Dr. Legge states that there are no cases of pitch warts or cancer among them. This is another piece of evidence against mechanical injury, for naphthalene soot and coal soot are similar as regards the physical nature of the particles, yet one is harmless and the other most dangerous.

OTHER TARRY COMMODITIES

Liquor carbonis detergens, creolin, etc., are used extensively on the skin. In some cases they cause thickening. They seem to promote the cell-proliferation of healing, and are used under prescription for this purpose. They contain the middle fractions of tar, which seem to be responsible for the proliferation which leads to the warts in the industries.

In this respect it may be useful to draw attention to the tar capsules which from time to time are advertised to be taken
internally as an aid to digestion. Those that have been tested in these laboratories also contain, as a rule, the middle tar fractions, and therefore it would appear advisable for them to be prescribed only with great caution. The intestinal epithelium is much more liable to malignancy than that of the skin, and subjecting it to a specific commodity is to be avoided.

There is no evidence that dust from the tarred roads causes warts, but there have been some complaints of conjunctival inflammation from it.

"SMARTING" OF THE FACIAL SKIN DUE TO PITCH DUST

This point may be conveniently discussed before we leave the tar products, although it is doubtful whether it is connected with the pathological changes which lead to pitch warts. As Mr. Lush points out (1), all fuel workers suffer from a burning sensation in the face especially when exposed to keen winds or sunshine, and one of the chief objections to the bathing regulations was that washing made this condition worse. The physical signs are not very noticeable; sometimes there is slight dermatitis with a little peeling, but never any discharge. There is never a "flare up" like that seen in eczema. The burning sensation is undoubtedly troublesome, coming on sometimes after an hour's exposure to the pitch dust—as the writer can personally testify—and it may last for several hours. The condition seems only to affect the cheeks and the region behind the ears, and it may be so bad as to prevent the men attending football matches.7

Some cargoes of pitch cause it more than others, and the bad varieties seem frequently to stain the skin a yellow color.

Experiments were made at the works to find out the cause of this burning of the skin. Some pitch was finely ground and then thoroughly washed with water and dilute acid; the water was allowed to dry on the skin, but no burning sensation could be felt. Two of the pitch grinders then rubbed the washed pitch

7 More recently this or a similar burning of the skin has occurred to a considerable degree among munition workers who handle certain coal-tar explosives. An acute dermatitis is produced, with a yellowish discoloration of the skin. The question is being investigated.
powder on their skins, when it was found that it still caused the dermatitis. It is apparent, therefore, that this burning is at least due in part to slight mechanical injury. A watery extract from some of the pitch which was more irritating than that from other cargoes, and which contained the yellow ingredient, did, however, cause a little smarting when applied to the dorsum of the hand, and it is possible that this is due to an excess of acridine.

But the common sites of the smarting are not those of the pitch warts; the lips, eyelids, and scrotum are not affected. It is possible that the slight mechanical injury may leave fissures in the skin in which the pitch dust may become impacted, and so lead to pitch warts, and the swarthy skin, which is due to "blackheads;" but the part played by it, for the reasons given above, is probably a minor one.

Attempts to protect the men's faces by fullers' earth was partly successful, but the men refuse to use it; protection by liquid paraffin caused such acute erythema that it had to be abandoned.

There is little evidence that smarting of the skin occurs among coal miners; soot appears to cause it only to a small extent. Dr. D. A. Crow has kindly interrogated 36 sweeps on this point, and has elicited the fact that 26 of them complained of slight burning, one saying that boiler soot from coke was particularly noxious. It may be due to the sticky nature of softened pitch and soot, which may necessitate tearing of the epithelium when washing it off.

PITCH FROM PITCH LAKE, AND FROM MANJACK MINES, TRINIDAD, WEST INDIES

Dr. H. L. Clare, the Surgeon General, Trinidad, has been good enough to supply the following information.

The Mines (Manjack) near Princes Town have not been worked since the beginning of the war. I have never heard of any unusual—or indeed of any incidence of cancer amongst the laborers; these mines are worked at a considerable distance below the surface, while the Pitch Lake work is all on the surface.
Dr. George Campbell, Resident Medical Officer of the Pitch Lake Company, reports to Dr. Clare, thus:

I have had no case of cancer among the pitch workers here during the last five years, and can find no history of such a case having occurred. I may say that the workers come very slightly into contact with the pitch, the actual process being largely one of cutting and loading. The pitch of the lake does not come from bituminous coal, but is closely related to the non-volatile constituents of crude oil, with no paraffin base. Composition: water and gas 29 per cent, bitumen 39 per cent, organic matter 7 per cent, mineral matter 25 per cent. Composition of the bitumen: carbon 82.33, hydrogen 10.69, sulphur 6.16, nitrogen 0.81.

The small content of nitrogen is most interesting, as will be seen later. The fact that the pitch is not bituminous is also worthy of note.

ANILINE DYES

There are practically no manufactories of aniline dyes of a large size in England, and it was difficult to obtain reliable information about industrial disease on the Continent, even before the war. The Chief Inspector of Factories, however, refers to a series of 14 cases of villous growth of the bladder in a works where the men were engaged in handling aniline dyes made there. Dr. Legge’s report of February, 1911, also states that dermatitis and eczema are produced by contact with several of the aniline colors—chrysoidin, Bismarck-brown, paranitranilin red, and others, but in none so markedly and so certainly as in the manufacture of dinitrochlorobenzene. In all the 16 cases referred to, dermatitis of the face, arms, armpits, and such parts of the body as are likely to be bathed in sweat, was the characteristic symptom, unaccompanied by any noticeable changes in the blood.

*The late Sir Henry Butlin, President of the Royal College of Surgeons, journeyed to the Continent expressly to ascertain the incidence of pitch-cancer at the briquette works. He returned with the information that the disease does not exist. Enquiry “through the trade” however, shows that it is about similar to the incidence in Great Britain.
PETROLEUM

There is no information that dermatitis or cancer is caused at the petroleum wells in America, Russia, or elsewhere; but absence of information does not necessarily mean that disease does not exist. At the shale oil* works in Scotland, however, paraffin dermatitis and cancer are not uncommon. Volkmann and Ogston's description, already quoted (see tar), also refers to the effects of paraffin. The two substances seem to produce very similar results. To judge from enquiry at the works, it is the crude paraffin which causes the trouble, and there have been some cases in the oil produced from cannel.

In his annual report, Dr. W. Walker, certifying surgeon for Mid Calder, states that during the year he has come across a few cases of "paraffin cancer" a disease from which shale oil workers are peculiarly liable to suffer, some more than others. It begins in a variety of forms, i.e., as an erythema, pimples, papules, etc.; these gradually dry, leaving hard crusts which, increasing in size, form hard, elevated, wart-like masses. As they increase in size these break down, and produce sloughing ulcers or paraffin cancers. He mentions three cases: (1) On the dorsum of foot, doing well after operation; (2) scrotal, so far doing well after extensive operation; and (3) back of wrist, necessitating amputation of the right arm at the shoulder. Enquiry by Mr. Brown (Edinburgh) elicited the following information as to the process of refining, so far as it affects the material handled in the press house, and as to the effect on the skin.

The shale is heated in vertical retorts, the gas being condensed, and the ammoniacal liquor separated from the oil by gravitation. The crude oil is distilled by heating and blowing steam through it, the result of the distillation being known as "green oil." The green oil is treated with 2 per cent sulphuric acid, and afterwards, in another vessel with 1 per cent caustic soda. The green oil already treated is again distilled with steam and fractionated, giving "light oil," "intermediate," and "heavy oils," the latter oils containing paraffin. The

* Shale and cannel are forms of coal.
light oil is treated with sulphuric acid and caustic soda, and then distilled, the result being "burning oil" which is ready for use, and "intermediate oil," which is added to the intermediate oil already obtained by the previous distillation of the green oil. The "heavy oil" passes through pipes to the cooling sheds, and is pumped through ammonia freezers and filter presses, the residue, in the form of a sludge or scale, being conveyed by a worm screw to the floor of the hydraulic press house. The heavy oil from the filters is re-treated with sulphuric acid and caustic soda, and again distilled and separated into "intermediate oil" and "lubricating oil." All intermediate and lubricating oils are then passed through coolers, freezers, and filter presses, and the scale is conveyed to the floor of the hydraulic press house by worm screw. It is this scale which causes the eruption on the arms of the workers. The men shovel the scale on to canvas cloths, which are laid in layers on bogies, the ends and sides of the cloths being folded over and the pile placed under the hydraulic presses. The liquid oil is pressed out and returns to the process again. The paraffin scale remaining in the cloths is shaken by hand into a melting pot, and blown into trays in sweating houses where it is purified by slow heat. It is then treated with animal black and is finally converted into wax. The men in the hydraulic press houses wear canvas bibs and leg coverings, but their arms are bare to the shoulders, and in handling the cloths they cannot escape coming into contact with the scale. The eruption usually takes the form of small pimples or red blotches, and is not painful unless these develop into boils. I examined the arms of 10 men of whom five showed warts, pimples, or scars.

The higher fractions, such as paraffin wax and "liquid paraffin" seem to be harmless. Indeed, liquid paraffin is consumed internally in enormous quantities as a purgative, and since its introduction as such during the last ten years there has been no such marked increase in intestinal cancer as one would expect if this substance caused a predisposition to cancer like pitch or soot. The higher refining process therefore evidently removes some noxious constituent.

Crude shale oil from some mines evidently cause more trouble than that from other mines, for several cases are reported from certain districts and none from others.
At the International Congress of Medicine in London, in 1912, Dr. Norman Walker showed some beautiful casts of paraffin dermatitis and epithelioma.

**VASELINE**

This is a petroleum fraction. It is used extensively on the skin to aid healing, and is said to increase the cell proliferation of healing.

**GREASE**

The manufacture of grease causes complaints similar to those produced by tar, but it requires no special comment here because they are evidently due to the tar oils which form a large constituent of commercial grease. Dr. Legge examined 31 men at grease works and found 6 suffering from pitch warts and 13 who had signs of old ones.

**KANGRI CANCER**

The “fire pot” is a wicker brazier having an earthenware center used by the natives in certain parts of India. It is carried inside the garments, as a rule suspended by straps over the shoulders. The fuel usually consists of decayed vegetable matter which forms a charcoal. The continual rubbing of this charcoal against the skin of the abdomen and thighs gives rise to thickening, ulceration, and epithelioma of the skin in much the same way as coal-soot and pitch.

**TOBACCO**

Smokers’ cancer of the lip is generally associated with mechanical injury caused by the rough stems of clay pipes, and the incidence is less than it was owing, apparently, to the introduction of vulcanite stems; but mechanical injury will not account for the high incidence of malignant disease of the larynx and fauces of men as compared with that of women, in whom this disease is rare. Tobacco, as it is smoked, consists of the partially dried leaf which has been allowed to ferment by putre-
faction. It is frequently mixed with olive oil (a substance which causes dermatitis in several trades), and is sold damped to various degrees with water. The drier the tobacco the more the smoke is inclined to “burn” the tongue.

**BETEL NUT**

The so-called betel nut that is chewed by natives in Madras, Ceylon, and the Straits Settlements is a mixture of betel nut, tobacco, and spices, which is allowed to remain in a warm place until it becomes putrid. It is the cause of epithelioma in the floor of the mouth.

**X-RAYS AND RADIUM RAYS**

Radiation need only be mentioned here as causing burns of an intractable nature. They lead to ulceration which is liable to malignant infiltration. So much has been written on this subject, that passing mention only need be made.

**ARSENIC CANCER**

Pye-Smith (3) has recently published a collection of 31 cases of this disease, giving an accurate description of each. He points out that in nearly all cases of arsenic cancer

It looks as if arsenic induces keratosis of the skin (as is now universally admitted), the keratosis mechanically inducing fissures, which readily become infected with bacteria and then ulcerate, the ulcers finally becoming cancerous.

He also suggests that arsenic may predispose the tissues generally towards cancer, a predisposition comparable to or even more marked than that caused by senescence; but it may be remembered that arsenic is a powerful cell-poison, and it may therefore bring about a result similar to that produced by old age, by causing cell-death.

It has been suggested that pitch cancer may be due to arsenic in the pitch. Tests made in these laboratories, however, have
failed to detect any arsenic in pitch. The pitch used at the briquette works has been raised to a temperature of 300°C before it is consigned there. The same remark applies to the suggestion that pitch cancer is due to turpentine. There is no turpentine in tar, pitch, or soot.

LEUCODERMA, KERATOSIS, AND CANCER

Lenthal Cheatle has drawn attention to the frequent incidence of malignant infiltration supervening on patches of atrophic skin which have become subsequently thickened. These areas may even be bilateral, and may in the first instance be caused by nerve disease. As in arsenic cancer, there seems to be a local destruction of cells followed by proliferation, which may ulcerate and ultimately become cancerous.

FOUL ULCERS

Old untreated varicose or syphilitic ulcers are prone to become malignant, as is well known. Since there are no figures available, it is difficult to ascertain with certainty whether the degree of suppuration does or does not increase this liability; but it seems common experience to find the malignant infiltration in the more neglected cases.

MANURE

Senile warts occur on the hands and arms of farm laborers who frequently handle manure. The Registrar-General’s returns for 1890–1892 show an incidence of 84 deaths as against 51 for all occupied males. In Germany agricultural laborers are especially subject to skin cancer.

When the foregoing commodities are examined collectively it becomes more apparent that mechanical injury per se can play only a minor part in the predisposition to occupational cancer. Apart from the evidence in this respect given by the coal-tar industries, the action of petroleum, arsenic, manure, tobacco, etc., also demonstrates it; for some of these commodities are solids, some are liquids, and physically they differ a great deal.
in other respects. Yet they all seem to bring about the predisposition to malignancy in a somewhat similar manner, namely, by becoming impacted in the tissues, where, by giving rise to cell proliferation, they produce a warty condition. The warts usually ulcerate at their bases and drop off, leaving an intractable sore. It seems to be the edges of the ulcers that become epitheliomatous, and there appears to be a specific liability, when the industrial warts are untreated, for this to happen.

Mechanical trauma, it is true, will predispose the tissues to malignancy, both carcinoma and sarcoma, a fact proved by clinical experience and by experiments on animals; but in occupational cancer it is clear that a chemical factor is also concerned which acts directly on the tissues, in the first instance inducing cell proliferation. If it were not so, apart from the evidence enumerated above, we should expect to find a similar incidence among chimney-sweeps and briquette makers as among stone-masons and metal-grinders, who work with even more gritty commodities, and yet who do not specially suffer. There must be a chemical factor responsible and the question is, what is it? It is true that x-ray cancer and the predisposition caused by scars, keloid, and degenerate nerve areas may be initially due to mechanical trauma, that is to say, to excessive energy or heat, or destruction following upon deficient blood supply, etc.; but these factors are not sufficient to account for the incidence of occupational cancer, and it is possible that the initial trauma in x-ray cases may also be followed by some specific chemical change in the tissues.

In conclusion, one further point may be mentioned. When the active commodities are examined collectively, it will be seen that all of them, with one exception, are products of, or are derived from, the products of the death and decomposition of living matter, although such death may have occurred centuries previously. Coal and its derivatives, including paraffins, charcoal, tobacco, betel nut, and manure, all have such a derivation; the one exception is arsenic, and that, being a powerful cell-poison, may possibly produce the products of cell death and decomposition in the tissues. It is important to bear this in
mind, although there is no actual proof that such products predispose the tissues to epithelioma; yet it is a striking point, for these commodities undoubtedly cause this predisposition when impacted for a long time in the tissues of the skin, whereas inorganic commodities, such as stone-dust and metal-dust, are ineffective. In this connection, it is useful to remember that carcinoma seems more frequent, in general, at sites which are continually subjected to organic matter undergoing bacterial decomposition, such as the rectum, stomach and indeed the whole intestinal tract), mouth, uterine cervix, breast (chiefly in women who have borne children), prepuce, anus, scrotum, etc. In sarcoma, on the other hand, this does not apply, any more than does the age incidence; but with occupational epithelioma especially, given that the predisposing cause of the disease is present equally in different parts of the body, it is usually in that part which is the dirtiest or which is affected with open ulceration that the malignant condition supervenes.

Decaying organic matter of all descriptions fertilizes living matter, and promotes cell proliferation, being used extensively for the growing of plants in agriculture. Up to a certain point, the more putrid the matter, the more pronounced is this fertilizing property. Soot is used by gardeners for this purpose, but it is only useful when it is wet, showing that it is necessary to dissolve something out of it, namely nitrogenous compounds. Mere grit has not this action. Ammoniacal liquor distilled from tar is a very valuable commodity, owing to the nitrogenous compounds it contains, being converted into artificial manures. The trade in nitrates for fertilization is enormous. Soot and tar products, in causing the cell proliferation leading to warts, would seem to act in accord with this principle, and epithelioma itself is also a growth consisting of an excessive cell proliferation.

To sum up: There seems to be some specific chemical agent responsible for occupational cancer; mechanical irritation plays only a minor rôle in this disease; and lastly, there is a probability that the mischievous agents are organic nitrogenous substances of a group common to all the dangerous commodities. In the coal-carbonisation—commodities, the fact that the coal is bituminous seems to be essential.
PART II

If one were to attempt to isolate a substance or a chemical grouping common to them all from the many and complex commodities that give rise to occupational cancer, one would be faced with a problem so vast that it would be futile to undertake it. The coal-tar derivatives alone would present an insuperable problem, for they contain a large number of substances of many varieties, including nitrogenous bodies of several descriptions. Besides, there would be nothing to go upon; one would not have the faintest idea how to start. One might fractionate gas-tar, pitch, or soot, but even then one would probably hit upon the wrong fraction and it would be impossible to correlate such a chemical analysis with a subsequent one made on tobacco-smoke, betel nut, manure, and any various compounds of arsenic which may in some way be produced by the drug in the living tissues. It may be remembered that arsenic is a "cumulative" drug.

After consideration it was resolved to attack the question from a point of view based on a working hypothesis. It is admitted that this principle of making facts—such as those given in the first part of this paper—harmonise with even a working hypothesis is illogical; but there was no alternative. The only way was to choose a reasonable line of argument, keeping all the facts known about occupational cancer and cancer in general always in view, and then to proceed experimentally.

First the facts known about cancer in general were reviewed, and then the more acceptable of the several theories and working hypotheses were studied to see how far they could be made use of in the investigation of occupational cancer. Some of the facts have already been alluded to in the first part of this paper, e.g., the remarkable age incidence of carcinoma (the form of disease with which we are immediately dealing), the common sites, the question of chronic mechanical irritation, and above all the phenomenon of excessive cell-proliferation which is a characteristic of malignant disease. But two other facts were also kept prominently in view, namely, the propensity
on the part of the cells to infiltrate surrounding tissues, and
the extraordinary fact that if the disease remains untreated the
subject of it emaciates and dies for some reason that has never
been satisfactorily explained.

The clinical data given in the first part of this paper un-
doubtedly justify the conclusion that, when dealing with the
cause of occupational cancer, we are in reality concerned with
two factors—a predisposing cause and an exciting one. The
predisposing cause is evidently a chemical derived from the
commodities when impacted in the tissues, but the exciting
cause seems only to appear when ulceration has occurred, espe-
cially if the ulceration occurs in the dirtier parts of the body.

The term ulceration, when used in this sense, is not a very
satisfactory one, for, although the classic definition "solution of
continuity of surface" seems always to hold good before the site
becomes malignant, the epitheliomatous condition invariably
appears at the growing (cell-proliferative) edge where there may
be no immediate loss of surface continuity, and the demarca-
tion between the benign and malignant proliferation may not be
clearly defined.

But there is a predisposing cause and an exciting cause
undoubtedly at work before a case of occupational cancer
becomes truly malignant. The specific commodity impacted
in the tissue giving rise to cell-proliferation like a wart; slough-
ing, leading to ulceration; more cell-proliferation at the edge with
ultimate infiltration, metastasis, and death. A definite sequence
of events.

On the face of these facts, therefore, the older theories did not
help very much. Take for instance the general hypothesis
that cancer follows on chronic irritation, in favor of which
there is considerable evidence. Let us analyse the expression
"chronic irritation." An irritant must be either mechanical or
chemical; a mechanical irritant must be due either to pressure or
heat, or to both. The hot stem of a clay pipe is an example; an
ill-fitting boot causing a corn which may become epitheliomatous
is another. What happens to the individual living cell in the
tissue which is subject to mechanical irritation? The term
“irritation” really is a clinical one; it has not a precise meaning to the cytologist. To the clinician the word implies a degree of injury as evinced by some reaction such as inflammation, pain, or itching, but there is no means of measuring the amount of injury suffered by the individual cell. Chronic irritation in a tissue is a definite condition, but when we discuss the individual living cell we had better use the generality—injury. “Injury,” surely, is the right word, because both heat and energy, if present in excess, will ultimately produce damage and even death (destruction) in a tissue. Irritation is merely a degree of this injury. So it must be with the individual cell. The cause of the irritation, as it increases, must sooner or later first damage and then kill the individual cells which constitute the tissue and which cannot run away. It is submitted, therefore, that when we speak of chronic mechanical irritation in a tissue, we are in reality dealing with a population of cells, some of which are normal, some damaged, and some dead, according to the degree of injury. If the chronic irritation is slight, there may be no death rate above the normal, but there may be damage to a certain number of cells. Presumably damage to a cell means death of portions of its protoplasm. The pathological term “degenerate cell” usually means vacuolation when it is examined intra-vitam.

A chemical irritant seems to fall into a similar category. Chemical irritants, if their administration is pressed, sooner or later become destructive agents. The word “irritation” here again means a degree of injury caused to the tissue by the irritant, namely damage or death to the individual cells as the case may be. If a substance is an “irritant” in certain dosage, it must become poisonous in greater dosage. A given chemical in given dosage can only have one of three actions on the living cell; it may be beneficial, inert, or injurious, i.e., poisonous. The chemical irritant must be a degree of the poisonous variety.

As regards mechanical irritation: The first part of this paper has shown conclusively that mechanical irritation per se cannot be responsible for occupational cancer; the coal-tar commodities alone prove the point. A specific chemical is concerned without
doubt. Is this chemical an irritant? is the next question. Obviously not, for it produces cell-proliferation, not destruction in the tissue.

Moreover, if occupational cancer were entirely due to chemical poisons derived from the commodities, we should certainly expect, for instance, a greater incidence of the disease among those who handle the lighter fractions of coal distillation, especially the phenol, creosote, and naphthalene fractions, than among those who handle tar or pitch. But these lighter fractions, although cell-poisons, are harmless as far as the predisposition to cancer is concerned. A striking contrast to the non-poisonous soot. Surgeons and nurses, whose hands are frequently immersed in concentrated solutions of mercury biniiodide do not suffer from cancer of the hands like those who are employed in handling paraffin at the shale works. Yet the mercury salt is infinitely more poisonous than anything contained in petroleum.

Trinitrotoluene and similar coal-tar derivatives used in munition manufacture, when impacted in the skin, cause dermatitis, and even atrophy of the liver, owing to their poisonous effects. Yet there has been no "flare" of squamous-cell epithelioma as a result of their action.

Nevertheless, apart altogether from occupational cancer, it must be admitted that chronic mechanical injury does give rise to a predisposition to malignancy, to wit—the clay pipe and the lip, the ill-fitting boot and the corn, the blow on the breast and scirrhus, the operation on the mole and melanotic sarcoma. Chemical injury also, in a similar manner, apart from occupational cancer, undoubtedly predisposes tissues to carcinoma, namely, chemical substances produced by inflammation as occurs in an erosion of the uterine cervix, syphilides of the tongue, etc.; these seem frequently to be due to chemical irritants of some degree.

But irritants are not nearly so powerful in their action as the occupational commodities. Neve, of the Kashmir Mission Hospital found 848 cases due to Kangri soot out of a total of 1189 squamous carcinomas. It is true that arsenic is a cell-
poison, and therefore might be classified among the "irritants," but the predisposition due to arsenic does not appear until years have elapsed after the patients have taken and have ceased to take the drug.

Injurious agents, therefore, both mechanical and chemical, by virtue of the degree of irritation they produce, by causing an amount of damage or death in the cell-population, may produce in a tissue a predisposition to cancer; but in occupational cancer something more is needed, namely a specific chemical which is contained in all the commodities themselves, and which sets up cell-proliferation (the wart) when impacted in the tissues.

The time honored hypothesis of Cohnheim does not harmonize with the clinical facts regarding occupational cancer. One could imagine, perhaps, that certain cells might retain a sort of quiescence from fetal days and then "light up" during senescence, although why these cell-rests, which are physiological components of the body, should ultimately destroy the patient, and incidentally themselves, is difficult to understand. One could even imagine that chronic mechanical injury might in some way cause the cell rests to "light up," but it is impossible to believe that those who grind gas-tar pitch in Cardiff should have cells included from birth, while those who grind blast-furnace pitch in Whitehaven should enjoy immunity. Cohnheim's hypothesis drives us to this reductio ad absurdum.

The same argument applies to the suggestion of Farmer, Moore, and Walker, which is based on the Weismann hypothesis of inheritance, and which, like Cohnheim's, does not divide the cause of cancer into predisposing and exciting origins. It is by no means proved that the cells of vertebrates are separated into somatic and reproductive varieties, and, even if that were the case, it is not probable that Indians who use the Kangri fire-pot should have more reproductive cells in the skin than those who become covered with shoe-blacking.

Shattock and Dudgeon have lately sought to advance the question by attacking the cause of cell-proliferation. They have suggested that cells multiply instinctively unless restrained by an antibody, and that pathological variation in the antibody
may produce tumors, etc. An antitoxin for an instinct is de-
cidedly new; but as a solution of the problem of growth, the
very premises of this hypothesis have never been proved; on the
contrary, some of the earlier experiments at Rothamsted Ex-
perimental Station have shown that plants, at least, become
barren if they receive no chemical stimulus from without.

The work of Roger Williams is of more assistance, for, apart
from the mass of information on cancer in general contained in
his book, he draws a suggestion from it that the immediate
nutrition of the cells may play a rôle in the causation of the
disease. The conclusions arrived at in the first part of this paper
appear to be somewhat in accord with this view.

On the whole, therefore, the well known hypotheses did not
offer a firm standpoint on which to base a series of experiments.
None of them offered any test to which the several commodities
that cause occupational cancer could be subjected. So it was
considered better to proceed on lines of work in which the writer
had been engaged for several years, investigating the causes of
cell proliferation. As pointed out in the first part of this paper,
cell proliferation is the first and a constant result of the action
of all the commodities which give rise to occupational cancer.

This working hypothesis was based on a series of experiments
which has produced evidence that, so far as certain groups of
cells at least are concerned, their division is due not merely to
instinct on the part of the cells themselves but to specific chemi-
cal agents, all of which appear to be amino substances set free
by cell-death. According to this hypothesis cells divide in
response to this stimulus from without; that is to say, the repro-
duction of cells is initially prompted by death occurring among
their neighbours, cell-death setting free the amino substances,
and the latter exciting cell-division among the surviving cells.

The hypothesis arose in 1909 from research with the jelly
method of in vitro staining, by which it was found that cell-
division can be induced in living human lymphocytes by mixing
watery extracts of dead tissues with the jellies on which the
individuals cells are resting. Subsequently the extracts were
made to induce division in leucocytes and certain epithelial cells
also.
Improvement in the test revealed the fact that the active agents in the watery extracts were nitrogenous substances produced by the decomposition of proteins, and several were isolated and proved to consist, among others, of some of the purin bases, such as creatin, xanthin, and tyrosin. For convenience the name auxetic\textsuperscript{10} was given to these cell-division-producing agents.

The action of auxetics on blood-cells was confirmed by R. Ross and again by Drew. Fantham succeeded in inducing division by auxetics in individual Entamoeba coli, the writer in the ova of Ascaris megalcephala, Drew in the spores of Polytoma granulosa, and in a fine series of experiments Cropper and Drew (4) have found that amoebae increase enormously in numbers in response to auxetics. Indeed the last authors have found that when individual amoebae are isolated from all other living creatures and placed in distilled water or on jelly containing only distilled water, they will not divide at all unless an auxetic be present, that auxetics will up to a certain point increase their proliferation according to the strength of solution, but that after a few generations have passed the presence of a ferment is also necessary if proliferation is to be kept up.

With these various classes of cells, then, auxetics undoubtedly prompt proliferation. When first the experiments with human white blood cells were published, it was disputed that the figures induced in lymphocytes were those of cell-division, because the jelly method revealed the fact that these figures, although they were in general principle those of mitosis, as far as lymphocytes are concerned, were dissimilar as regards what is generally believed to be the nucleus. But estimations of increase in numbers by precise methods, together with the work of Cropper and Drew and others, seem to settle this point, for the cell-division which they induce in amoebae is of the normal type.\textsuperscript{11}

Since certain human and some other cells will divide in re-

\textsuperscript{10} The name implies an excitor, which in its turn may and has been interpreted to mean a stimulant; but it is debatable whether they are such or whether they are foods. Without doubt, some are foods.

sponse to auxetics, and since these auxetics are produced in a tissue by cell-death, the working hypothesis was extended to cell-proliferation which is frequently the predisposing cause of cancer. Injury gives rise to cytolysis and to the cell-proliferation of healing, and if it becomes chronic, proliferation to the extent of production of benign tumor formation may be brought about. In order to test the last point, auxetics were introduced into the mammary ducts of goats' breasts—using a blunt hollow needle to prevent injury—and adenomatous nodules were produced.

The working hypothesis, therefore, had a basis founded on experimental facts. Cells had been made to proliferate both in vitro and in vivo by means of auxetics. Healing of a damaged site presumably is brought about by auxetics set free by the injurious agent, the amount of proliferation being in ratio to the amount of damage, a theory which seems to be a reasonable one.

Some preliminary experiments were then made with soot and with gasworks and blast-furnace pitch. Using living human lymphocytes as the test cells and employing the jelly method, it was possible to detect auxetics in the soot and gasworks pitch, but only to a very slight degree, if at all, in most varieties of blast-furnace pitch. Later on, H. Bayon succeeded in producing a condition resembling the early stages of squamous epithelioma in rabbits' ears by injecting watery extracts of gasworks tar and pitch. Similar extracts of blast-furnace pitch, on the other hand, used in a similar way, did not produce this result.

The jelly method further showed that most of the alkaloids excited amoeboid movements in leucocytes and some forms of epithelial cells, an observation originally made by Osler, and the term kinetic was given to such substances. It was found that many kinetics, although they do not themselves induce cell-division, have a power of augmenting the action of auxetics in doing so. If an auxetic is present, the addition of a kinetic may increase the action of the auxetic as much as five fold, as can be measured by the quantity of auxetic present. Choline and
cadaverine (pentamethylene diamene), products of putrefaction, are powerful augmentors as well as kinetics, acting in this way like the alkaloids.

All the occupational commodities were then tested for auxetics and kinetics, and some of them for augmenting the former. The cells used were human lymphocytes for auxetic and augmentor, and human leucocytes for kinetic action.\footnote{A complete description of the experiments together with the technique will be found in the Brit. Med. Jour., 1911, 1, 884, and 1913, 1, 511; and in Researches into Induced Cell-reproduction and Cancer, vols. I-III, (London and Philadelphia), 1911 and 1913.}

**SOOT**

A 20 per cent watery extract contains both auxetics and kinetics.

**BLAST-FURNACE PITCH**

A 10 per cent watery extract contained a trace of kinetic only, and auxetic could only be detected if this action were artificially augmented by an alkaloid such as atropine.

**GAS-WORKS PITCH**

A 10 per cent watery extract contained both auxetics and kinetics.

**GAS-TAR**

A 10 per cent watery extract contained both auxetics and kinetics.

**BLAST-FURNACE TAR**

A 10 per cent watery extract contained no auxetic or kinetic.

There is, then, an experimental difference between blast-furnace tar and pitch and the ordinary gas-works varieties, which is in accordance with the clinical evidence. As already stated, there are two explanations for this difference, one being that blast-furnace tar (and therefore the pitch) is chiefly derived from the less bituminous Scottish coal, the other being that it is pro-
duced at a lower temperature. Samples of coal from various seams were therefore tested. They were sent to the laboratory distinguished by numerals only, the key being kept at the Mines Department of the Home Office until the tests were complete. It was found that coal does not contain nearly so much auxetic or kinetic as do tar, pitch, or soot. High concentrations had to be made in the extracts (ten times higher than tar) before any action could be detected; and the more bituminous coals contained auxetics and kinetics, while the harder varieties contained only traces or none at all. This seems to be the explanation why blast-furnace tar and pitch contain less auxetics and kinetics. From this time onwards all experiments were of the “blind” variety.

In order to control the foregoing experiments, and to ascertain which fractions of tar are responsible for the auxetics and kinetics, a series of experiments was made with thirty-two samples of tar, pitch, and various oil fractions derived from them. The difference between blast-furnace tar and pitch and the gas-works varieties was again detected, and it was demonstrated that the auxetics and kinetics are contained in the middle fractions of tar. The lighter oils, such as the naphthalene and creosote fractions, are free. It was also found that the auxetics in tar become volatile at about 350°C.

These facts correspond with the theory at the works that the mischievous elements are in the anthracene fraction, but since anthracene itself is not an auxetic, it is evident that the auxetics are impurities in that fraction.

Mrs. Norris, working in these laboratories, has recently been able to isolate two auxetics from tar. One is a substance apparently identical with pseudocumidine, which is only a feeble auxetic, the other is an active base, having an empirical formula \( C_{2n}H_{4n}O_{n}N_{n} \), but nothing is known as to its constitutional formula.\(^9\)

Hence the auxetic and kinetic content of tar and its derivatives seems to harmonize with the incidence of the disease

\(^9\) Note on the bases of gasworks coal-tar which are believed to be the predisposing cause of pitch cancer with special reference to their action on lymphocytes together with a method for their inactivation. Biochem. Jour., 1914, viii, 253.
caused by these commodities; the more concentrated they become, the more auxetic and kinetic they contain up to a certain point when the auxetics become volatile. Unfortunately this point, 350°C., is too high for a serviceable pitch to be prepared, or the problem at the briquette works would appear to have a simple solution. Such a pitch is too hard and contains too much carbon for it to be used as a binder for briquettes, and its caloric value is greatly reduced. The auxetics, being soluble, can be washed from the tar, but this also was objected to by the trade because of difficulty in removing water from tar. Its presence causes deterioration of the pitch and danger from explosion during distillation.

OTHER TAR PRODUCTS

Certain tar antiseptics contain auxetics, and some of the capsules advertised for internal administration also have this action.

Naphthalene, which is converted into the harmless shoe-blacking, has not this action.

PETROLEUM

Some samples of commercial refined paraffin oil (kerosene) contain auxetics, and vaseline also has this action. A series of "interim oil scales" and heavy lubricating oil fractions from Oakbank, Addiwell, and Broxburn, in Scotland have been tested. None of them apparently contain auxetics, but four out of seven contain kinetics, and three out of the four kinetic samples are also augmentors.

TOBACCO

Tobacco contains auxetics. Ten per cent watery extracts of ordinary pipe tobacco showed this action to a considerable degree, many cells exhibiting division figures when the 10 cc. of jelly contained 1 cc. of the extract. The water in a "hubble bubble" pipe, through which tobacco smoke had been drawn from 50 grams of several forms of prepared tobacco, also gave an auxetic reaction, but a watery extract of a cigar did not appear so active, it requiring a greater strength of extract.
Soon after kinetic action was first observed with the jelly method, it was found that arsenic salts in some strengths excited amoeboïd movements in leucocytes, and Pye-Smith's recent investigations have prompted more experiments with them. Like the heavy petroleum fractions, certain arsenic compounds are not auxetics, but some of them are augmentors when added to organic auxetics. Arsenic oxide, salvarsan, atoxyl, and sodium arseniate are all kinetics, the first being the most active, the last the least. When extracts of meat were used as the auxetic, the first three compounds proved to be augmentors in the order named as regards strength, but the sodium salt was negative. The jelly on which the cells were spread required at least 3 cc. of a 1 per cent solution of the arsenic compound to produce this augmenting action. But no such action occurred with an artificial auxetic such as theobromine.

By itself, then, arsenic does not appear to produce cell proliferation, but in the presence of products of cell death—such as the extract of meat used in the experiments—it augments the action of the auxetics contained therein. It is possible that chronic skin eruptions due to arsenic are caused by this action. The oxide is the most active salt in vitro, but there is no evidence as to the combination in which the drug is held in the living tissues.

ANILINE DYES

Many of these, especially methylene blue, azure I and II, eosin, neutral red, etc, have an auxetic action on blood cells in vitro, and when injected into tissues in vivo also produce cell proliferation. In view of the fact that their chemical constitutions are so different, it is probable that they produce this action by causing cell death in the first instance, the cell death in its turn setting free auxetics. Cells will live with their granules stained, but their death occurs as soon as the intranuclear chromatin is reached by the stain.
These all come into one category. Auxetics can be detected in decaying organic matter, and, if the putrefaction has progressed, kinetics with augmentation are also present. Drew has recently tested pond water for these actions, and has found them increased after the cell death of the winter, suggesting that they are responsible for the awakening of pond life in the spring. There seems to be a relationship between the content of auxetics and albuminoid ammonia. It was with a putrid extract of a dead tissue that cell division was first induced in lymphocytes in 1909. But if the putrefaction has progressed beyond a certain degree, poisonous substances are produced which cause cell death.

Experimentally, therefore, the action of the commodities can be explained by the auxetics or augmentors contained in the commodities themselves. They become impacted in the tissues, either in the hair follicles or the sebaceous glands, or perhaps in fissures caused by slight mechanical injury. Auxetics are dissolved out of the commodities and set up cell-proliferation, giving rise to thickening and warts. The warts slough and drop off, leaving an open ulcer, in which the over-prolific cells at the edge are prone to become malignant. The malignant invasion, judging by clinical evidence, seems to be due to some additional factor, possibly connected with production of more kinetics, which excite amoeboid movement and still further augment the proliferation. From the clinical evidence in occupational cancer, the additional factor appears to come from without. The apparent necessity for open ulceration, and the fact that it is the dirtier parts of the skin which are more liable to the disease, are points worthy of consideration, although the suggestion is as yet entirely theoretical and there is no absolute proof that it is correct.

Auxetics are produced as age advances, the physiological increase of cell death during senescence having this result. It is part of the working hypothesis that the predisposition to cancer
during senescence may be due to a predisposition to cell proliferation caused by auxetics physiologically free in the tissues in general. And, as already pointed out, so may it be with mechanical and chemical injury; the predisposition to cancer brought about by them may also be due to the auxetics set free locally by the trauma. But in occupational cancer, in addition to the auxetics produced by any mechanical or chemical trauma, there are also those contained in the commodities themselves which would produce, and which actually seem to produce, a greatly increased if not a specific predisposition.

The unsatisfactory part of the above work, however, is that it is based on a working hypothesis. There is always a danger, when working in this way, of being biased in favor of a hypothesis; but in this case there was no alternative, and all the experiments were “blind” ones. Since one cannot distinguish by appearance between varieties of tar, pitch, and oils, the experimenters had no idea which was under investigation at any given time; and it is remarkable how accurately the results of the experiments harmonized with the clinical facts. Still, when elaborating such a hypothesis, even though, as in the case in point, it is based on direct experimental evidence, great care must be exercised to prove each step. In the cancer problem, unfortunately, this is not easy, for it involves so many other problems; e.g., the cause of the reproduction of living matter, of development, metastasis, of death, etc., about which very little is known, so that, at present, as regards occupational cancer, one can only work on the somewhat empirical lines described in this paper.

It should be remembered, therefore, that although there is experimental proof that auxetics stimulate the proliferation of cells, a gap is jumped if we assert that they predispose a tissue to cancer, for there is no definite proof of this. It is true that by auxetics cells may be made to divide when removed from the body; and it is true that auxetics, when artificially inoculated into animals, will produce proliferation amounting to benign tumors, and if continued with augmentation will produce a condition identical in microscopic appearance with epithelioma.
It is also true that benign tumors, in a wide sense, form a predisposing site for cancer, and equally true that the auxetic theory coincides with the clinical evidence. But we cannot assert that this is the way in which the predisposition is caused naturally in the living tissues. Proof cannot be obtained owing to lack of methods. The jelly method enables us to test the action of chemical substances on individual living cells in vitro; Carrel and Burroughs have shown how to grow cells in tissue formation in vitro; and sectioning will show the arrangement of cells after death. But there is no method by which we can see with chemical-detecting eyes, so to speak, into a living tissue in its natural surroundings. Therefore we cannot see whether, or how, auxetics work, except under experimental conditions.

An effort is being made, however, to prove the auxetic theory by destroying those substances in tar on a large scale, and observing whether this destruction prevents the incidence of warts and cancer at the briquette works. Mr. H. W. Robinson, of Messrs. Robinson Brothers, tar distillers, West Bromwich, has suggested that the application of the Sorensen reaction might be practicable. Formaldehyde inactivates amino substances, and tests have proved that it destroys the auxetics in tar. Three years ago this was tried on a considerable scale. Messrs. Bird and Son, Cardiff, prepared a large quantity of pitch made from tar treated with formalin, and this pitch was used exclusively at one briquette mill of the Crown Preserved Fuel Company at Cardiff. It was originally intended for this experiment to continue for six months, but unfortunately, owing to unforeseen circumstances, a mechanical breakdown occurred at the tar-distilling works, and the experiment came to an end in two months. The time was too short for the medical commission, who were nominated by the Home Office, and who had previously examined the men's skin, to offer an opinion on the result. The war then broke out, and the shortage of formaldehyde prevented a resumption of the experiment. But the government has promised to undertake it anew as soon as possible, and it is to be hoped that it will then be carried out on a larger scale, the whole of one briquette works to use nothing
but treated pitch for one year (about 50,000 tons) and the other works to act as controls.

If the destruction of auxetics in tar leads to the prevention of occupational cancer at the briquette works, it would appear that the case against auxetics is established.

**POSTSCRIPT**

Since this paper was written, the writer has seen an excellent paper by Dr. Walter J. Heiman in the Journal of Cancer Research, 1916, i, 343, on "Precancerous dermatoses." It complains that the expression "precancerous" is misleading. True, the term is wrong; as Dr. Heiman points out it implies a constant forerunner of cancer. But the expression is not common in Great Britain, and the writer never heard it mentioned in the United States seven years ago.

As was mentioned in the discussion of chronic irritation, many lesions, whether caused by physical force (mechanical injury) or by chemical action (poison), undoubtedly lead to cancer, some occasionally, some more frequently; but it does not necessarily follow that every mechanical or physical trauma is always followed by cancer. Especially in medicine, one can take stock phrases too literally. "Predisposing" seems to be a better term than "precancerous," implying as it does liability, or a more frequent occurrence than usual.

It seems probable, therefore, that the majority of the dermatoses and conditions to which he refers are probably the result of chronic injury (mechanical or chemical) and might be classified as such; but the more occupational predisposition, as already shown, falls into a different category from a clinical point of view, in that a malignant outcome is more constant and the commodities themselves contain or produce a definite predisposing agent.

Kangri cancer is not due to burns only, as Dr. Heiman assumes, but also to the remarkable form of soot which is rubbed into the burn. It is not a little dangerous for Dr. Heiman to draw deductions from his thirteen cases, for the Pearson-Poisson
formula would show a large error of random sampling. But when he states that "we lack a control, a standard of comparison" he strikes a true note, which the writer thinks applies to many issues in cancer research.

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