FILE NAME: Shell (SHEL)

DATE: 1950

DOC#: SHEL024

DOCUMENT DESCRIPTION: Book Excerpt - Environmental Cancer and Petroleum

Shell

ARTICLE 3

Environmental Caner and Petroleum

CKNOWLEDGMENTS

van Heiningen for valuable discussions
iklijke/Shell Laboratorium–Amsterdam

ferences.

k, R. W. "A.P.I. drilling and production
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1948, **44**, 537
ppl Mech., 1946, **13**, A 101.

Geol. Inst. India, Dec., 1936, **32**, 1.
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ENVIRONMENTAL CANCER AND PETROLEUM.*

By Lt.-Col. S. J. M. Auld, O.B.E., M.C. (*Past-President*).

Modern industrial civilization has brought in its train many added dangers to mankind. Not the least of these are the occupational diseases resulting from exposure to conditions arising in the course of manufacturing operations. Sometimes such adverse effects come from the absorption of definite poisons. In that case steps can be taken for the purpose of ameliorating the environmental conditions. In any event the course of the specific poisoning can often be followed and knowledge built up for the prevention and treatment of the ailment concerned. That is particularly the case where the poison is recognizable and is quick in action.

Where the effect is slow or a lengthy latent period exists, culminating in sudden and often apparently unrelated illness, recognition and control of the disease is more difficult. That is generally how it happens with environmental cancer—with cancer indeed as a whole, where the initial impetus given to the uncontrolled cell growth which constitutes the disease is often unknown because of the long latent period which follows.

That is regrettable, for, with few exceptions, the causes of cancer so far discovered are of external origin. It is, unfortunately, also true that at the present time only a fraction of 1 per cent of all cancers can be traced to known causes. To be able to trace the origin of any cancer is, consequently, of the greatest possible value in the building up of our defences in what the whole world is realizing is the greatest battle of all time which man has had to wage.

It is for such reasons that the appearance in this field of the petroleum industry is to be whole-heartedly welcomed. The oil industry is the most highly organized and most scientifically controlled of all the world's great industries. The fact that its direct participation in the causation of cancer appears to be small is of little account compared with its resources for the collection and recording of data; and in particular its ability to trace effects to identifiable materials, to conditions of production and to methods of handling or application.

In order to show how the oil world is helping to-day, and largely in Great Britain, in establishing a link between cause and effect at least in occupational or environmental cancer, it is necessary first to sketch in the background of proved or suspected causes of environmental cancer, and to proceed therefrom to the particular case of the hydrocarbons and their association with petroleum and its application.

The author's position must be made clear to prevent any misunderstanding. He is not a medical man or a biologist, and his association with this subject is that of an oil technologist. However, for many years he has helped to represent the petroleum industry, through the Institute of Petroleum, the Petroleum Board, and the Ministry of Fuel and Power,

* An address to the Northern Branch of the Institute of Petroleum, January 17, 1950.

in their various joint discussions with Government and other bodies concerned with the subject. He can, therefore, discuss the subject with some knowledge and authority, but must emphasize that his specialized interest is that of oil.

Known Causes of Cancer.

The recognized and established carcinogens are generally either physical or chemical in nature. The physical include α-, β-, γ-, and X-rays, and ultra-violet light.

The chemical list is a long one, and is continually being extended. Hueper [1] has classified them approximately as in Table I.

Table I.

Inorganic.	Organic.
Arsenic	Aromatic amines. Aniline *
Chromates	Benzole. Polycyclic hydrocarbons
Nickel carbonyl	Soot. Carbon black. Tar and pitch
Asbestos	"Paraffin oil." Shale O.I. Mineral Oils
Beryllium *	Anthracene oil. Creosote
	Azo dyes *
	Oestrogens *

* Conflicting evidence.

These are placed in Table II in their chronology of discovery, with notes added as to the investigator, the organs affected, and the nature of exposure.

Table II
(After Hueper)

Name.	Date.	Discoverer.	Organs affected	Nature of exposure.*
Soot	1775	Pott	Skin (scrotum)	Occ. (chimney sweeps)
Arsenic	1822	Ayrton	Skin	Occ., env.
Paraffin oil	1875	Volkmann	Skin	Occ. (lignite and shale oil industry)
Shale oil	1876	Bell	Skin	Occ.
Pitch and tar	1876	Vanouvrier	Skin	Occ.
Crude oils (scale)	1879	Härting and Hesse	Skin	Occ.
Sun (ultra violet)	1893	Unna	Skin	Occ. (farmers, sailors)
Aromatic amines	1895	Rehn	Bladder	Occ. (dye industry)
Röntgen rays	1902	Frieben	Skin	Occ., med.
Schistosoma hematobium	1911	Ferguson	Bladder	Env. occ. (Egypt)
Röntgen rays, radium	1911	Von Jagicz, schwartz, and Von Siegenrück	Bone marrow (leucæmia)	Occ., med.
Anthracene oil	1913	Rauchonsek	Skin	Occ.
Betel nut, tobacco	1915	Davis	Mouth	Habit (India, Malay)
Diet *deficiency*	1919	Monchet and Gerard	Liver	Env. (poverty diets, Africans, Chinese)
Radium	1920	Leitch and Sequira	Skin	Occ., med.
Lubricating oils	1922	Southam and Wilson	Skin	Occ. (mule spinners)
Creosote	1924	Cookson	Skin	Occ.
Benzole	1928	Delore and Bergamo	Bone marrow (leucæmia)	Occ.
Uranium	1929	Lowry	Lung	Occ.
Radioactive rays	1931	Martland	Bone	Occ., med.
Chromates	1932	Alevens	Lung	Occ.
Nickel carbonyl	1932	Stephens	Nasal sinuses, lung	Occ.
Asbestos	1934	Wood and Gloyne	Lung	Occ.
Radioactive rays	1934	Neitzel	Lung	Occ., med.
Tar fumes	1936	Kahawata	Lung	Occ.

* Occ. = occupational; env. = environmental; med. = medical.

Important and interesting as [illegible] mental causation, those tabulated [illegible] our problems are soot; paraffin [illegible] benzole, anthracene oil, and creosote [illegible]

Attention is directed to the fact that "[illegible] oils," which in any case is a vague [illegible] the subject of our special interest, [illegible] chemicals are recognizably aromatic [illegible] conditions of heat which presage their [illegible] applies even to the so-called "paraffin [illegible] to be the cause of cancer amongst [illegible] industries. In general, it applies also [illegible] outskirts of our province, like the azo dyes.

The original observations from which [illegible] emanate are those of the celebrated [illegible] St. Bartholomew's Hospital, and record [illegible] His diagnosis has already been quoted [illegible] his important address to the Royal Inst[illegible] and Cancer.[3] It refers to Pott's recognit[illegible] as a specific disease, concerning which he

> "It is a disease which always m[illegible] first appearance in, the inferior part [illegible] duces a superficial, pruntul, ragged [illegible] rising edges. The trade call it soo[illegible] people seems singularly hard, in th[illegible] frequently treated with great brut[illegible] cold and hunger, they are thrust [illegible] chimnies, where they are bruised [illegible] and when they get to puberty beco[illegible] noisome, painful and fatal disease.
>
> "Of this last circumstance there [illegible] perhaps it may not have been suffi[illegible] generally known.
>
> "The disease, in these people, se[illegible] lodgement of soot in the rugæ of the [illegible]

This tremendously important obser[illegible] one hundred years. Reports then bega[illegible] other forms of cancer in workers connec[illegible] These, together with reports from the [illegible] "mule-spinners' cancer" of the cotton [illegible] of industrial, or at any rate occupational, [illegible]

Since 1915, when Japanese workers first [illegible] for the laboratory examination of carcin[illegible] been ever-expanding observation and rec[illegible] things, frequently chemical, encountered [illegible] observed incidence of cancer. Thus, in [illegible] gressively shown that raw tar, and then [illegible] 400° C, contained the carcinogenic mate[illegible] This was quickly followed by the recogni[illegible]

Important and interesting as are many other of the forms of environmental causation, those tabulated which have a particular bearing on our problems are soot; paraffin, and shale oil; pitch, tar, and tar fumes; benzole, anthracene oil, and creosote; and lubricating oils.

Attention is directed to the fact that, with the exception of "lubricating oils," which in any case is a vague term chemically speaking and is largely the subject of our special interest, all of these organic materials or individual chemicals are recognizably aromatic in nature or have been formed under conditions of heat which presage their content of such substances. This applies even to the so-called "paraffin oil," shown by Volkmann in 1875 to be the cause of cancer amongst workers in the lignite and shale-oil industries. In general, it applies also to the organic chemicals on the outskirts of our province, like the azo dyestuffs and the aromatic amines.

The original observations from which our present-day lines of enquiry emanate are those of the celebrated surgeon Percivall Pott, F.R.S., of St Bartholomew's Hospital, and recorded by him as far back as 1775.[2] His diagnosis has already been quoted at length by Prof. J. W. Cook in his important address to the Royal Institute of Chemistry on Chemistry and Cancer.[3] It refers to Pott's recognition of chimney-sweepers' cancer as a specific disease, concerning which he says:—

> "It is a disease which always makes its first attack on, and its first appearance in, the inferior part of the scrotum; where it produces a superficial, painful, ragged, ill-looking sore, with hard and rising edges. The trade call it soot-wart. . . . The fate of these people seems singularly hard; in their early infancy, they are most frequently treated with great brutality, and almost starved with cold and hunger; they are thrust up narrow, and sometimes hot crannies, where they are bruised, burned and almost suffocated; and when they get to puberty become peculiarly liable to a most noisome, painful and fatal disease.
>
> "Of this last circumstance there is not the least doubt, though perhaps it may not have been sufficiently attended to, to make it generally known.
>
> "The disease, in these people, seems to derive its origin from a lodgement of soot in the rugæ of the scrotum."

This tremendously important observation lay practically dormant for one hundred years. Reports then began to appear regarding skin and other forms of cancer in workers connected with the coal-tar industry. These, together with reports from the shale-oil industry, and later the "mule-spinners' cancer" of the cotton industry, indicated the existence of industrial, or at any rate occupational, origin of specific forms of cancer.

Since 1915, when Japanese workers first used modern biological technique for the laboratory examination of causative agencies of cancer, there has been ever-expanding observation and recording of data connecting actual things, frequently chemical, encountered in the industries concerned with observed incidence of cancer. Thus, in the coal-tar industry it was progressively shown that raw tar, and then particular fractions boiling above 400° C, contained the carcinogenic materials which were being sought. This was quickly followed by the recognition, due to their freedom from

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scovered.	Organs affected.	Nature of exposure.*
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	Skin	Occ., env.
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	Skin	Occ.
ᵴ	Skin	Occ.
nd Hesse	Skin	Occ.
	Skin	Occ. (farmers, sailors)
	Bladder	Occ. (dye industry)
	Skin	Occ., med.
	Bladder	Env., occ. (Egypt)
z, Schwartz, and	Bone marrow (leucæmia)	Occ., med
hancock	Skin	Occ.
k	Mouth	Habit (Arabs, Malay)
nd Gerard	Liver	Env. (poverty diets, Africans, Chinese)
Sequira	Skin	Occ., med
and Wilson	Skin	Occ. (mule spinners)
	Skin	Occ.
d Bergamo	Bone marrow (leucæmia)	Occ.
	Lung	Occ.
	Bone	Occ., med
	Lung	Occ.
	Nasal sinuses, lung	Occ.
Gloyne	Lung	Occ.
	Lung	Occ., med.
	Lung	Occ.

v. = environmental; med. = medical.

nitrogen and sulphur, that the most active bodies concerned were in fact hydrocarbons.

Biological Testing.

It is as well at this stage to explain the test procedure used by the biologists in determining the extent and course of cancerous activity.

The tests are made on living animals—chiefly mice, rats, rabbits, guinea-pigs, dogs, and monkeys. The most extensively employed are mice—partly because of their susceptibility, partly because of the relative rapidity with which results can be obtained.

The question must arise in the minds of oil men, or scientists in other spheres of training and activity, whether the disease so induced in animals is the same or similar to human cancer, and whether the effects are or are not generally otherwise comparable. Also, in respect of the reproducibility of the tests, their quantitative sufficiency, and the satisfaction by statistical procedure of elimination of other known or unknown conditions which might affect the conclusions to be drawn. All of these matters are of extreme importance in biological tests in a way much less known to the chemist and physicist, whose aims to produce like results from like conditions are comparatively simple in the matter of choosing the conditions.

In the past these points greatly concerned those oil technologists who were drawn into consideration of the problem of carcinogenesis: they have satisfied themselves that the procedure is standard and fully accepted; that the standards are scientifically high—that is, they are fully organized in detail and understanding like those, for example, of the methods of the Institute of Petroleum. This important matter might be summed up to the lay technical man by saying:

> (*a*) The results are generally repeatable and reproducible. Even if there were nothing else to the procedure, this would constitute it a valuable observation and non-committal test.
>
> (*b*) The pathological effects produced are constant and closely similar to those of spontaneous and human cancer.
>
> (*c*) Difference of susceptibility or, as we might say, the response, of the various animals is recognized; and in the event of check-testing being needed animals up to and including the primates are available (Table III).

Tests on mice, as being the first, greatest, and best-organized screen, are therefore very important. The great laboratories use mice by the thousand. They are bred from constant, suitable, strains, and are used, or should be used, at the same approximate age and condition of health—and, of course, fed, housed, and generally looked after identically. In a modern laboratory they are, as test materials, approximating the standardization of chemical test reagents.

One aspect of this biological test technique to which attention needs constantly to be paid is the quantitative or statistical side. Even with the quick-living mouse, a series of tests requires about a year for completion. This is a big proportion of a mouse's life. It is necessary, therefore, to use enough mice for any test, and at the same time to know

Agent.	Organ.	
Soot	Skin	Rabbit,
	Lung	Mouse
Shale oil	Skin	Mouse
	Lung	Mouse
Pitch and tar	Skin	Mouse, gu
Anthracene oil	Skin	Mouse
Lubricating oils	Skin	Mouse
Creosote	Skin	Mouse
Benzole	Bone marrow	Mouse *
Tar fumes	Lung	Mouse
β-Naphthylamine	Bladder	Dog

* Conflicting ev

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The Carcinogenic H

The recognition that extracts from
tars were themselves carcinogenic stimu
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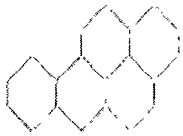
the pioneering work of Sir Ernest Kenn
produced tars was important by directin
aromatic hydrocarbons, and encouraging
causes of coal-tar cancer. Eventually, it
tracked down in coal-tar pitch a strongly
benzpyrene (Fig. 1). From 2 tons of pi
7 g of the material.



3:4-Benzpyrene.

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TABLE III.

Reproduction of Occupational Cancers in Animals.

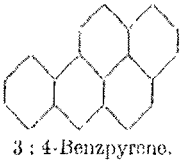
Agent.	Organ.	Species. †	
Soot	Skin	Rabbit,[4] mouse	
	Lung	Mouse	
Shale oil	Skin	Mouse	
	Lung	Mouse	
Pitch and tar	Skin	Mouse, goat, rabbit, dog	Monkey
Anthracene oil	Skin	Mouse	
Lubricating oils	Skin	Mouse	
Creosote	Skin	Mouse	
Benzole	Bone marrow	Mouse *	
Tar fumes	Lung	Mouse *	
β-Naphthylamine	Bladder	Dog	Rabbit, goat, mouse

* Conflicting evidence.

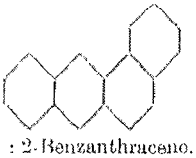
sufficiently the past history of their strain, so as to be able to allow for all the natural ills to which they are prone. Because of the long time required for the tests, extrapolation of the results must be very tempting when the quantitative factor is found insufficient. That might happen as a result of starting out with insufficient living subjects or because of some experimental disaster. But any extrapolation, or filling up of gaps for that matter, can obviously be very dangerous. It is for those reasons that biological tests must be conducted on a vast scale and with meticulous care in respect of such conditions as *can* be controlled.

THE CARCINOGENIC HYDROCARBONS.

The recognition that extracts from soot and from cancer-producing tars were themselves carcinogenic stimulated interest in the search for single chemicals capable of producing malignant tumours. In the search the pioneering work of Sir Ernest Kennaway on carcinogenic artificially produced tars was important by directing attention towards the complex aromatic hydrocarbons, and encouraging the search for the individual causes of coal-tar cancer. Eventually, in 1932, Cook and his co-workers tracked down in coal-tar pitch a strongly carcinogenic hydrocarbon, 3 : 4-benzpyrene (Fig. 1). From 2 tons of pitch they were able to separate 7 g of the material.



3 : 4-Benzpyrene.



1 : 2-Benzanthracene.

FIG. 1.

The " tracking down " of this hydrocarbon was done by a method which has more than academic interest. It may readily be brought to the

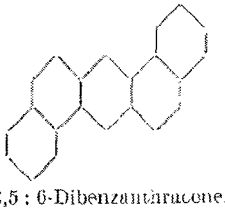
attention of oil men and questions asked about it. It is *fluorescence*. It had been observed by Maynecord and Hieger, who collaborated with Cook, that the carcinogenic tars were all strongly fluorescent and possessed fluorescence spectrum bands of similar position and distribution. Here was a possible quick clue, without having to wait for the results of biological tests each of which involves many months or years to complete. Concentration of the extracts using this means of control eventually resulted from a variety of methods, including the chromatographic, in the separation of the 3 : 4-benzpyrene described. This has a closely related structure to 1 : 2-benzanthracene (Fig. 1) which, though itself inactive, has a similar type of fluorescence spectrum, partly in the visible. This synthetic material is the parent hydrocarbon from which nearly all the highly active carcinogenic compounds of this kind are derived.

It is clear, then, that although fluorescence accompanies the general structure of the hydrocarbons belonging to this important carcinogenic grouping there is no relationship between fluorescence and carcinogenicity. *First*, there are many known carcinogens which are not fluorescent at all. *Secondly*, although the active hydrocarbons of this kind are largely fluorescent, the reverse is not the case as is seen from 1 : 2-benzanthracene itself. *Thirdly*, it is not fluorescence in general which is characteristic, either visible or under ultra-violet light, but the analysis of the spectrum and its classification.

These are points to be borne in mind, since as a result of Hieger's important work ill-advised generalizations have sometimes been made and suggestions offered, in respect of oils and other materials, to use fluorescence as a classification of carcinogenicity and as a guide towards the use of particular materials.

Of the many hundred derivatives of 1 : 2-benzanthracene which have been prepared, many are inactive, others only slowly active, and others again very powerful. It depends largely on the position of substitution and the nature of the substituting groups. Generally, the higher the substituting homologue the lower the carcinogenic activity. Small differences in structure may have very big effects on carcinogenicity.

The first compound of this class found to be cancer producing was 1 : 2,5 : 6-dibenzanthracene (Fig. 2).



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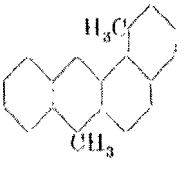
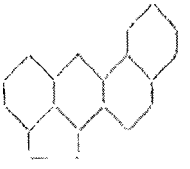


9 : 10-Dimethyl-1 : 2-benzanthracene.

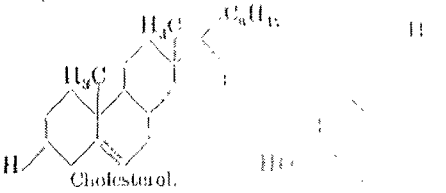


Cholanthrene.

FIG. 2.

One of the most powerful is 9 : 10-dimethyl-1 : 2-benzanthracene (Fig. 2). Others may contain nitrogen, sulphur, five-ring groupings, or incompletely closed rings. Cholanthrene (Fig. 2) is of interest as being a powerfully active carcinogen related to cholesterol (Fig. 3), and the sex-hormones

oestrone and testosterone (Fig. 3) [illegible] components of the human body.



Cholesterol.

FIG. 3.

Other polycyclic hydrocarbons of the [illegible] have also been synthesized and shown to [illegible] realized that these are also asymmetrical in structure from the benzpyrenes and [illegible]

The skin tumours produced by these compounds are truly malignant, and [illegible] *spontaneous and human cancers.*

That is the real answer to the very [illegible] significance of this synthetic work. There [illegible] in *multiplying the number of hydrocarbon* of inducing cancer in experimental animals [illegible] results are consistent and repeatable [illegible] in the *study of the form of occupational* cancer, as well as in throwing light on the [illegible] of cancer in the human body. Whether such [illegible] *intermediates in spontaneous human cancer* relationship between them and body matter [illegible] is a matter for speculation. But it is obvious [illegible] *must be opened wide—and everything* will [illegible] scrutiny.

There are, then, two great reasons for [illegible] relationship to the cancer problem. The [illegible] believed will be a relatively short-term [illegible] the oil industry; and there is the possibility [illegible] thoroughly organized research and study [illegible]

It may be reiterated that such a small [illegible] can be traced to actual cause that it is of the [illegible] clues should be followed up inexorably. [illegible] industries, petroleum is of small importance [illegible] must be repeated that this relatively slight [illegible] importance because of the highly organized [illegible] varying chemical nature of the crude oils and [illegible] the widespread use of petroleum products [illegible]

The oil industry has been concerned in the following ways :—

(a) *Occupational.*

(1) Amongst paraffin-wax workers, [illegible]

(2) Amongst lubricating-oil users [illegible]

(3) In the use of cutting oils.

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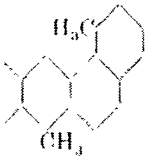

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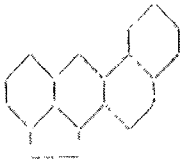

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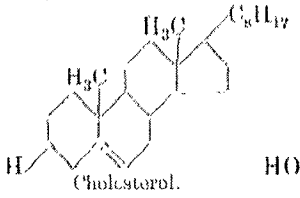
10-dimethyl-1 · 2-benzanthracene (Fig. 2), phrur, five-ring groupings, or incompletely . 2) is of interest as being a powerfully olesterol (Fig. 3), and the sex-hormones

oestrone and testosterone (Fig. 3), all of which are, of course, normal components of the human body.



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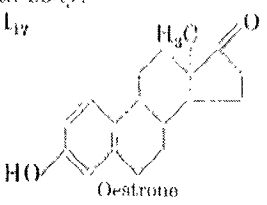
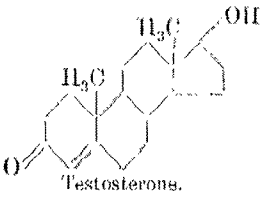


Oestrone



Testosterone.

FIG. 3.

Other polycyclic hydrocarbons of the phenanthrene and chrysene series have also been synthesized and shown to be carcinogenic, but it will be realized that these are also asymmetrical ring compounds, not dissimilar in structure from the benzpyrenes and benzanthracenes.

The skin tumours produced by these synthesized or natural chemical compounds are truly malignant, and indistinguishable in nature from *spontaneous and human cancers*.

That is the real answer to the very natural question of what is the significance of this synthetic work? There would in itself be little point in multiplying the number of hydrocarbons and other compounds capable of inducing cancer in experimental animals. But the mere fact that the results are consistent and repeatable may have the greatest importance in the study of the form of occupational and generally environmental cancer, as well as in throwing light on the course and ultimately the cause of cancer in the human body. Whether such substances are concerned as intermediates in spontaneous human cancer, or whether there is any relationship between them and body materials of apparently allied structure is a matter for speculation. But it is obvious that here is a door which must be opened wide and everything within subjected to the most careful *scrutiny*.

There are, then, two great reasons for the study of petroleum in its relationship to the cancer problem. There is the attack on what it is believed will be a relatively short-term problem—occupational cancer in the oil industry; and there is the possible application of the results of thoroughly organized research and study to the cancer problem as a whole.

It may be reiterated that such a small proportion of all human cancer can be traced to actual cause that it is of the highest importance that such clues should be followed up inexorably. In comparison with many other industries, petroleum is of small importance in cancer causation. But it must be repeated that this relatively slight connexion may be of great importance because of the highly organized industry involved, the greatly varying chemical nature of the crude oils and the processes concerned, and the widespread use of petroleum products throughout the world.

The oil industry has been concerned in the ætiology of skin cancer in the following ways :—

(a) *Occupational.*

(1) Amongst paraffin-wax workers, in shale.
(2) Amongst lubricating-oil users as mule-spinners' cancer.
(3) In the use of cutting oils.

(b) *Experimental.*

(1) As selective-solvent extracts.
(2) In cracked oils of low volatility.

It is not proposed to consider these subjects *seriatim* or chronologically. It will be more to the point to look at those regarding which there has been most discussion. Many of the matters of broader interest will then arise in passing. But first it must be pointed out that both epidemiologically and experimentally those portions of petroleum concerned are within the higher boiling ranges. So far there is no suggestion that carcinogenicity is directly concerned with the volatile low-boiling or intermediate products such as gasoline, kerosine, and gas oil. Nevertheless, that does not exclude the hydrocarbons which may be present in such fractions. Benzene itself, under certain conditions, is not free from suspicion, despite the fact that it is a chosen solvent of the biologists for the application of carcinogens to experimental living subjects.

At present potential petroleum carcinogens appear to be concerned chiefly with those fractions generally known as: (*a*) the wax distillates, and (*b*) the lubricating-oil residuums. These, in effect, cover the whole lubricating-oil range, with a boiling point from say 300° C upwards. The range would include the lowest-viscosity spindle oils up to those practically non-volatilizable at ordinary pressures, like the heavy machine oils.

It is also to be noted that the list includes on the one side shale oil and cracked fractions which have been subjected to high temperatures for their fundamentally reconstructive production, and on the other side lubricating-oil distillates and residues which by premise have not been chemically changed during fractionation, or the slight changes in which have been negated in the normal course of refining.

The distillation range in both classes would, of course, cover the possible occurrence of those carcinogenic hydrocarbons—naturally known, synthesized, or yet to come which have been referred to.

Paraffin Wax and Shale Oil.

The light oils and wax derived from shale oil have long been recognized as causes of skin cancer. Bell in Edinburgh reported scrotal cancer of a shale worker in 1876, and Volkmann is quoted by Leitch as recognizing skin cancer as a result of shale and lignite occupation in Germany one year earlier.

Dermatitis is known to occur amongst the shale-paraffin workers, but there is no record of petroleum operators with paraffin wax having been subject either to dermatitis or cancerous growths.

It is most likely, even in shale, that the irritant or active constituents are not part of the wax, which is paraffinic by nature as well as by name, but rather of the oily coloured components accompanying the slack wax. These are known to be chemically reactive, and are not necessarily allied in nature to the crystalline paraffin wax. Indeed, Berunblum has extracted from Blue Shale Oil the same 3 : 4-benzpyrene as Cook identified in coal-tar pitch.

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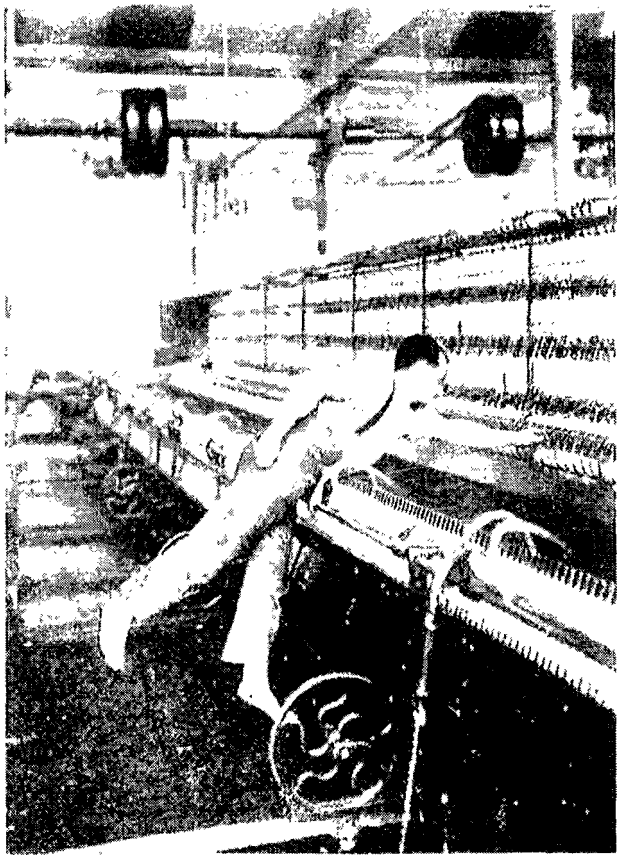

FIG. 4.

Mule-spinners' Cancer.

The occupational disease of mule-spinners' cancer has attracted much attention in the U.K. It is indeed around mule-spinners' cancer that much of the interest and concern in petroleum carcinogenicity has revolved. Its history is already a trifle obscure, but it appears to be the case that Southam and Wilson in 1922 drew attention to the high incidence of scrotal cancer in Lancashire mule-spinners, and that in 1924 Leitch was able to produce tumours in mice by applying solutions of the lubricating oils involved. Mule-spinners' cancer is a skin cancer, epidemiologically associated with the occupation of cotton-spinning with the mule (Fig. 4). Operators who succumb, generally do so after a long period of working under the conditions prevailing -sometimes over twenty years. The disease may attack various parts of the body, but like soot cancer and paraffin cancer is frequently associated with the scrotum.

The conditions of operation are of importance, and have been recorded by Dr E. M. Brockbank,[4] who says :—

> " The spinner works bare-footed in vest and overall trousers without any shorts between them and the skin. As the illustration shows, he leans over the mule to join or piece with the thumb and finger the broken ends of a thread of yarn . . . The scrotum constantly comes in contact with oil on the trousers. The vast majority of men piece with the left hand, and for this reason the left side of the scrotum is affected a similar number of times. . . ."

The temperatures in the mule-spinning rooms are excessive, and may exceed 105° F.

Brockbank also quotes Home Office records (Table IV) giving information on the incidence of the disease over some selected years.

Table IV.

	Spinners and piecers.	Cases per 1000.	Total cases.	Total deaths.
1926	48,029	1·83	88	20
1930	46,714	1·75	82	21
1936	32,232	1·27	41	12
1940	23,009	1·78	41	10
1946	17,671	2·03	36	21

He points out that the increase in number of cases per 1000 in recent years is due to the greater proportion of older spinners at work, and the greater liability of cancer of any form to occur.

Manchester Committee on Cancer.

As a result of the observations of Southam and Wilson and the work of Leitch, the Manchester Corporation some years later, in 1928, set up a large committee further to investigate cancer in general, and mule-spinners' cancer in particular. Experimental work was placed under the direction of Dr C. C. Twort and the cancer research committee under the

chairmanship of Dr E. M. Brockbank. Reports were published annually, and accounts of the researches published in the medical Press. These confirmed the observations of Leitch, and supported his conclusions that mule-spinners' cancer is caused by carcinogens present in the lubricating oil used.

This work was substantially subsidized by the oil industry notably by the Shell Group, the Anglo-American Oil Company, and the Anglo-Persian Oil Company.

In 1934 the Manchester Committee proposed a standard for mineral oils to enable the textile industry to choose lubricants which should be

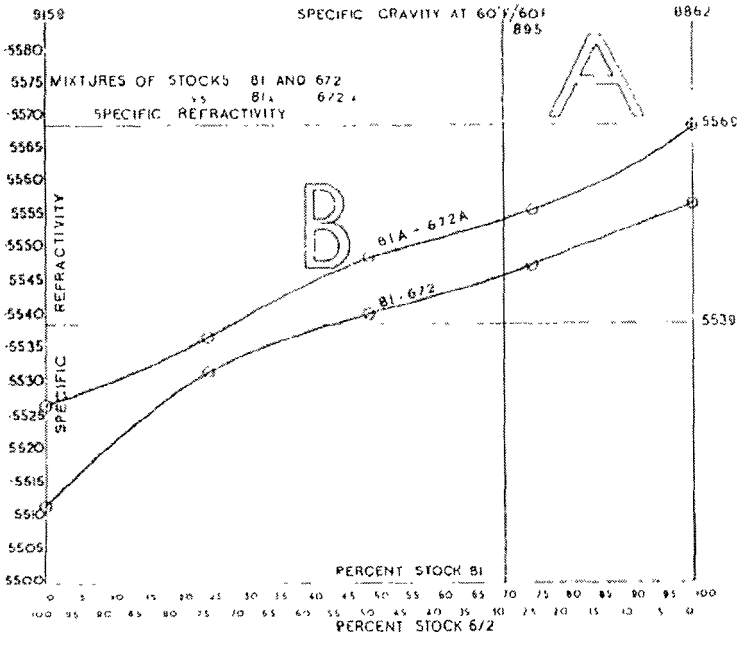

FIG. 5.

substantially free from carcinogenic properties. The criterion was believed to render tests on mice obsolescent, and consisted of a believed relationship between carcinogenicity and the refractive index and specific gravity of the lubricating oil. The specification read :—

> "Mule-spindle mineral lubricating oils should have a specific refractivity below 0·5539 when the specific gravity is above 0·895, or a specific refractivity below 0·5569 when the specific gravity is below 0·895. By specific refractivity is meant $\frac{n}{d} - 1$, where n is the refractive index for d-line sodium light, and where d is density in grammes per millilitre at 20° C."

In view of the importance of the subject, Committee's conclusions were natural.

Data showed this specification to [illegible] m blends of paraffinic (Oklahoma) oils, curves, and check-curves cross (the horizontal) and specific gravity (cent that blends between 45 and 71 per cent 71 per cent in the other are dangerous stocks would be safe. Many other sim complete lack of acceptability of the s made clear that "extent of refinement, to line up with "degree of carcinogenic the specific refractivity/density relations

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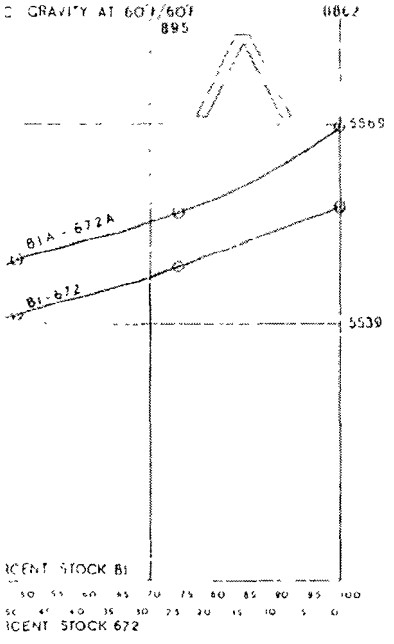

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In view of the importance of the subject, the validity of the Manchester Committee's conclusions were naturally closely examined.

Data showed this specification to be unsound. For example (Fig. 5) in blends of paraffinic (Oklahoma City) and naphthenic (Gulf Coastal) oils, curves, and check-curves cross the specification limits of refractivity (horizontal) and specific gravity (vertical) in such a way as to indicate that blends between 45 and 71 per cent in one case and between 29 and 71 per cent in the other are dangerous, whereas all other blends of the same stocks would be safe. Many other similarly collated data also indicated complete lack of acceptability of the specification. In addition, it was made clear that "extent of refinement" the characteristic most likely to line up with "degree of carcinogenicity" goes in the opposite direction to the specific refractivity/density relationship when applied to paraffinic oils.[5]

By this time, however, it was over late. The too-much publicized Manchester Formula for "non-cancerous oils" had understandingly, but wrongly been widely accepted as the complete solution to the problem. This was unfortunate for several reasons :—

(*a*) The textile workers, the employers, and to an appreciable extent the medical profession were being misled as regards the facts of the case, and possibly lulled into a false sense of security. Blends of oils such as those described were by no means unlikely to exist in practice.

(*b*) The oil industry found the Manchester specification unacceptable, and many oil scientists felt that insufficient attention was being paid in the textile industry to *prevention* by cleanliness, working conditions, medical inspection, change of occupation for workers susceptible to skin trouble, and so on.

These things were known, from the petroleum industry's own experience with shale oil and occupational oil dermatitis, to be of the first importance. Indeed, paraffin dermatitis and paraffin cancer were already regarded in the shale industry as being under control and largely confined to the older men who had contracted them years previously. Also, results both in the U.K. and in the U.S.A. in the control of cutting-oil dermatitis, by systematic washing and other regularized forms of cleanliness and in the application prior to working of protective creams and ointments, were very encouraging.

Another point which seemed to support this form of approach to the problem was that enquiries in other countries—including the U.S.A., France, and India—failed to disclose the occurrence of occupational cancer in their textile trades when working under apparently similar conditions and with similar oils to those in Lancashire.

(*c*) It meant that insufficient attention was being paid to the development—or rather the testing and use, of truly non-carcinogenic oils. It had been apparent to many oil men that more drastic refinement—possibly by solvent extraction, or by treatment with such agents as might be expected to destroy the carcinogens, was the most logical approach to the problem as far as the lubricating oil was concerned.

(*d*) It delayed consideration of systematic examination of petroleum for the purpose of separating the actual carcinogens and study of their chemical structure and properties.

Wartime Conditions

In 1943–44 arose two matters of some significance in placing the study of the carcinogenicity of petroleum on the right lines. The first was the bringing to notice by Twort of the possible carcinogenic, or otherwise noxious effect of lubricating-oil extracts, which under war conditions were in use as substitutes for extenders, plasticizers, and binding materials which could no longer be obtained.

The second was an approach to the Petroleum Board by the Federation of Master Cotton Spinners' Associations and the Amalgamated Association of Operative Cotton Spinners and Twiners, asking that oils to the Manchester Specification be made available to the textile industry. In making this request they quoted the Manchester Committee as stating ". . . testing of oils from cotton mills for carcinogenicity has been practically discontinued, as all mineral oil being generally used is pooled and is a mixture of oils. . . ." This, of course, was not at all the way in which the Lubricating Oil Pool actually operated! But it gave the Petroleum Board the opportunity of summing up the situation, and pointing out that oils to the Manchester specification had not been asked for during the previous four years of war either by distributors or users; that such oils could undoubtedly have been supplied if wanted, and the Board was prepared at once to set aside oils meeting the specification in two ranges of viscosity—despite the fact that the efficacy of the specification was questioned. At the same time the Ministry of Fuel and Power drew attention once more to the need for the improvement of operating conditions in the cotton mills.

These two matters obviously tied up together. If, by solvent refining oil stocks from which lubricating oils are made, the extracts were more carcinogenic than the original stocks, then the refined oils must be less so. This conformed with the oil industry's past views, and the Petroleum Board arranged to finance biological testing and research on the matter at Birmingham University. Work was initiated by Prof. Haswell Wilson and Dr D. L. Woodhouse in the Cancer Research Laboratory in the Department of Pathology and under the ægis of the British Empire Cancer Campaign Committee,

After about twelve months' investigation and testing of petroleum extracts, interesting results were obtained to which separate reference will be made.

White Oils.

Throughout the extended study of the relationship of lubricating oil to mule-spinners' cancer the question of extent of oil refining has cropped up frequently. As far as the oil is concerned this has always been the chosen aspect to the problem of the chemist and oil technologist From quite early days Twort expressed belief in white or medicinal oils being the least carcinogenic of all he tested, sharing immunity in that respect with fatty oils. The possibilities of removing reactive carcinogens from mineral oil by earth treatment, oxidation with air or chemicals, solvent extraction, acid treatment, were co
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extraction, acid treatment, were all discussed, but nothing was done. That possibly was due to the limited testing facilities available, the amount and expense of the work involved, and lack of a sense of realism perhaps in those most intimately concerned.

In the early days of 1946, however, the step was taken by the Manchester Oil Refinery Group, in conjunction with Twort, of definitely recommending the use of technical or medicinal white oils as spindle oils for mule spinning. These oils are selected petroleum distillates heavily treated with sulphuric acid or oleum.

The proposal was brought to the attention of the Petroleum Board, whose advisers were quickly alive to the logic of the suggestion, and recommended that, if a *prima facie* case could be made out for the non-carcinogenicity of such white oils, they should at once be made available to the textile trade as spindle oils. Examination disclosed that the evidence available was meagre. Nevertheless, at a meeting called by the Ministry of Labour and attended by representatives of other ministries, the textile trade, and the petroleum industry, the decision of the Ministry of Fuel and Power to make white oils available as textile lubricants was confirmed, despite the scarcity and dollar cost of such oils at that time. Simultaneously, the Petroleum Board announced its further financial subsidy of research work on the subject at Birmingham to supplement the very limited information on which the decision had been made.

With the exception of a few more letters and articles in the trade journals, once again nothing happened for another extended period—nearly two years. There were practically no enquiries for the white oils and no demands for supplies—either from consumers or distributors.

In 1948, however, the Master Spinners and the Cotton Operatives again called into being the *ad hoc* Committee of 1946, with the addition of representation from the Shirley Institute. By this time there was fortunately corroboration by Woodhouse of Birmingham of the biological inactivity of white oil samples submitted by the Petroleum Board.

Decisions were thereon made by the Federation of Master Cotton Spinners' Associations to standardize on the use of white oils subject to practical tests showing them to have suitable lubricating value.

Such mill trials, carried out with plain white oils and white oils blended with fatty oil, all of comparable viscosity, showed satisfactory performance and unexpectedly very little difference amongst themselves as regards power consumption.

The *ad hoc* committee concerned has since achieved an official basis by being brought under the control of the Factory Department of the Ministry of Labour and National Service.

WHITE OIL SPECIFICATION.

It was remitted to the petroleum industry representatives to submit a specification to cover suitable white oils for adoption by the trade. This has now been done, and the draft specification is in the hands of the Committee, by whom it may be expected to be published at an early date.

The specification is based primarily on definition of nature and pro-

duction, and upon colour. It is recommended that colour should be of the highest standard known, as representing the most drastically refined oils, and consequently those likely to be the least carcinogenically active.

Later, when further testing and investigation has been carried out, it may be possible to relax the standard without danger. This joint action of the cotton and petroleum industries, with the support and understanding of the Government, is a fine example of co-operation for the common good. It makes up somewhat for the period of misunderstanding and diversity of action of the past. Expenditure of time and money, and ultimate cost of the very special oil concerned, have been no obstacle in dealing with this aspect of the fell disease.

As far as can be seen at present nothing further can be done as regards the oil.

There may, however, be unforseen snags, and it is essential there should be no false feeling of safety. It is most sincerely to be hoped that nothing will interfere with the campaign for cleanliness, for protection by means of clothing and barrier creams, and for better conditions of operation. The recommendation of the Joint Advisory Committee of the Cotton Industry (1945) for the adoption of automatic wiping-down motions and non-splash devices is good as far as it goes, but no layman can but wish that mule spinning, with its attendant conditions as described by Dr Brockbank, could be exchanged for other methods of spinning less exacting.

Fatty Oils.

Statements to the effect appear from time to time in the technical and trade Press that animal and vegetable fatty oils are non-cancerous. Twort has recorded all such oils tested by him as being innocuous; but he has also pointed out that oleic and linoleic acids (which may, of course, be present to an appreciable extent in commercial fatty oils and to a small extent even in well-refined oils) are capable of producing non-malignant tumours in mice. They are also capable of amplifying the cancer-producing effects of certain chemical compounds.

It has also been stated that when using sesame oil as a carrier for chemical carcinogens the blanks with sesame alone were not free from activity.[3]

These matters are mentioned, as the specification for white oils referred to may factually or tacitly permit compounding. In this it would be in line with the observations of the Manchester Committee. It is well to realize, however, that there is no full clearance for fatty oils, and in view of the difficulty of defining their nature and their purity the author would suggest limitation of their use until further work has been done.

All concerned would wish to express their appreciation to Dr C. C. Twort for his devotion to his purpose of eliminating mule-spinners' cancer. The single-mindedness of Twort and his co-workers—and of the Manchester Committee as a whole—has been responsible, both directly and indirectly, for much of the progress made.

Carcinogenicity of Oil Extracts.

The work of Woodhouse at Birmingham on behalf of the Petroleum Board, to evaluate the carcinogenicity of oil extracts, covered materials

from stocks derived from different crudes and treatment. Such treatment is by selective solvents. These remove the ring-type compounds, which include susceptible constituents, so that the oil is less prone to oxidation for example, and is more stable to oil.

The materials tested at Birmingham, derived variously from :—

Venezuela (Colon, Lagunillas, etc.),
U.S.A. Gulf Coast (West Beaumont),
Colombia,
Equador,
Middle East (Persia),
U.K. (Eakring).

The solvent-extraction processes used (Solocto), Edeleanu (benzol/SO_2), and [illegible].

Altogether, twelve petroleum extracts over a period of some twelve months tested, and gave almost always compared by check-tests with known chemicals normally used in plastics industry.

The results varied quantitatively, but showed that solvent refining tended to carcinogens in the extracts. The less activity than corresponding coal-tar products already in use. Nevertheless, should be used with circumspection especially avoiding continual bodily co

Recently some attention has been directed extracts as *core oils in foundries* to products less readily obtainable. The such recent use of extracts and a cancer amongst foundry workers, but possibility of all decomposition products temperature being carcinogenic.

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from stocks derived from different crudes by various processes of solvent treatment. Such treatment is a process of physical extraction with selective solvents. These remove the more aromatic and naphthenic-ring-type compounds, which include many of the more chemically susceptible constituents, so that the raffinate is much more resistant, to oxidation for example, and is more paraffinic in nature than the original oil.

The materials tested at Birmingham were all products from feed-stocks derived variously from :-

Venezuela (Colon, Lagunillas, Concepcion, and Tia Juana),
U.S.A. Gulf Coast (West Beaumont),
Colombia,
Equador,
Middle East (Persia),
U.K. (Eakring).

The solvent-extraction processes concerned included Duosol (propane/Soleeto), Edeleanu (benzol/SO_2), and furfural.

Altogether, twelve petroleum extracts of different kinds were tested over a period of some twelve months. A second series of confirmatory tests followed, and gave almost identical results. The first series were compared by check-tests with known carcinogens and with certain chemicals normally used as plasticizers and extenders in the rubber industry.

The results varied quantitatively from one material to another, but showed that solvent refining tended, where they existed, to concentrate carcinogens in the extracts. The most active were lower in biological activity than corresponding coal-tar products and less noxious than certain materials already in use. Nevertheless, it was apparent that such products should be used with circumspection and under controlled conditions, especially avoiding continual bodily contact

Recently some attention has been directed towards the use of petroleum extracts as core oils in foundries, taking the place of linseed and other products less readily obtainable. There can be little connexion between such recent use of extracts and a believed above-normal incidence of cancer amongst foundry workers, but it draws fresh attention to the possibility of all decomposition products of organic matter at high temperature being carcinogenic.

CUTTING OILS.

In a recent paper by Dr Cruickshank and Prof. Squire[6] attention is drawn to the possible effects of exposure to mineral oils of workers in engineering processes; and particularly to the use of cutting oils in automatic machining. Under these conditions workers are susceptible to oil folliculitis (inflamation of the hair follicles), and the great majority become affected. Moreover, about one-third of those examined contracted warts of one of two kinds. These warts are of a type known amongst tar-

workers and mule-spinners. There were in addition some cases of precancerous skin condition and one of scrotal cancer.

These observations may have to be regarded as warning signs, and certainly call for study and amelioration where possible of the conditions of operation. It seems to be the case that whilst a little of the cutting oil may be oxidized at the tool edge, the considerable loss of oil known to occur in use is due to the formation of very fine spray which deposits on the surroundings, including the operators, as a thin film. The initial inflammation is mostly on the hands and forearms, but clothing becomes charged with oil, and the general conditions in this respect are not dissimilar from those met in mule-spinning.

The conclusion to be drawn is that if improperly dealt with continuous exposure to cutting oils is a hazard. This is supported by certain epidemiological data and also by biological tests. Magnification of the effect is undoubtedly caused by irritation from clothing, injury, and abrasion from metal particles, and in this respect falls within the class of action of oil and other occupational dermatitis, to the avoidance of which much attention is nowadays paid in factories.

In this connexion Cruickshank and Squire urge stricter methods of prophylaxis—reduction of actual skin contamination by oil, improved anti-splash devices, and use of more suitable clothing; higher standards of cleanliness, organized use of effective barrier creams; regular medical inspection; and attention to personal susceptibility.

To those interested in the nature and use of barrier creams a previous paper by Cruickshank [7] on the subject of their evaluation may be recommended. As protectives, the soapy type of oil-resistant barriers seem to be of limited effect, and have the disadvantage that when after a limited time they are penetrated by the mineral oil they give no aid to subsequent removal. Greasy protectives, on the other hand, rapidly mix with the contaminating oil, but do assist subsequent cleansing.

In view of the dubious nature of some of the protective components, it is clear that a great deal more work is required on the subject.

Cracked-oil Products.

Modern refinery practice is largely concerned with the reconstitution of petroleum hydrocarbons by means of heat and catalysts. Under the conditions of cracking and reforming, most of the new products are molecularly relatively simple. But there is always a small proportion of heavier materials formed by re-condensation and polymerization. These, when distillates, may range in boiling point up to the gas oils and light fuels. They are preponderantly aromatic in character, and having been subjected to heat treatment are not readily susceptible to heat. Their molecular-weight range, for example M.W. 230–250, would include that of many of the hydrocarbon carcinogens previously mentioned. In view of their nature and mode of origin it is not surprising that biological testing has shown some of these fractions to possess carcinogenic activity. This has resulted in the suggestion being examined by the medical section of the American Petroleum Institute, to which reference will be made later.

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ORGANIZATION OF RESEARCH.

Institute of Petroleum Research Group No. 2.

The work sponsored at Birmingham University by the Petroleum Board started by biological testing of white oils and petroleum extracts. An account of this work is contained in a paper by Woodhouse and Irwin.[8]

It had been determined by the Petroleum Board's advisers, however, that work on the carcinogenicity of petroleum should be put on a fundamental basis as soon as possible. For this purpose the Board promised the necessary funds, and arrangements were made with Birmingham University to undertake the biological side of the research work involved. These arrangements were well under way when the Petroleum Board was dissolved. Amongst its last activities the Board, with the concurrence of the Ministry of Fuel and Power, approached the Institute of Petroleum to accept responsibility for continuation of the work, and offered a substantial sum to initiate the research. It was implicit that further financial support, when needed, would be forthcoming from the individual oil companies.

The Institute accepted the responsibility, and implemented it by the formation (under its Research Committee) of Research Group No. 2, over which the author has the honour to preside.

The Group consider that work embarked on should not be of an applied or *ad hoc* nature, but an endeavour to separate and identify the active components present in petroleum and determine their properties. As there are hundreds of different oilfields and many hundred different crude petroleums, it is necessary to be realistic and make a limited choice. This choice is governed by :-

(*a*) Difference of type and distribution.
(*b*) Importance in extent of production.
(*c*) Content of lubricating-oil fractions, since carcinogens, where already indicated, had occurred in the heavier distillates.
(*d*) Supplies being the complete and untreated crudes.
(*e*) Authenticity and repeatability of experimental supplies.

Medical Research Council.

Quite separately, as a result of the attention paid to mineral-oil carcinogenicity, the Medical Research Council at the end of 1948 set up a Committee with the terms of reference :-

> "to initiate and carry out research into the carcinogenic action of mineral oils and compounds of other origin with which they may be combined in use."

The Medical Research Council, it should be explained, is a body of the Privy Council, and as such possesses all the powers necessary to embark upon such action.

The Committee thus formed is of high calibre, and includes specialists in cancer pathology, the chemistry of cancer, biological testing, statistics, and petroleum technology. The various ministries concerned have also nominated representatives to attend as may be required.

The M.R.C. Committee works closely with I.P. Research Group No. 2,

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with ultrasonic oil emulsions are an indication of the existence of ameliorative properties in some forms of petroleum, or even in the petroleum carcinogens themselves.

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