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COPY FROM D. V. S. FOR PERSONAL INFORMATION OF MEMBERS OF MEDICAL ADVISORY COMMITTEE AND ITS SUBCOMMITTEE ON CARCINOGENICITY

ESSO LABORATORIES
Standard Oil Development Company
P. O. Box 51, Linden, N. J.

January 11, 1955

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

I am attaching recent minutes of the Committee on the Carcinogenic Action of Mineral Oils received in this office from Dr. Newquist. I believe that the agenda of this meeting, that the first page of attachment A, that attachment B and attachment C would be worthwhile duplicating and forwarding to the members of the Medical Advisory Committee and the Kettering Laboratory group. Also, I believe the report entitled MRC.54/880, CAMO.54/17 as well as MRC.54/875, CAMO.54/16 would be worthwhile duplicating and distributing to the members of the Medical Advisory Committee and the Kettering Laboratory group.

I was particularly interested in report MRC.54/880, CAMO.54/17 since it is stated in that report that the relative potency of D-1953-54 compared with that of D-1952-53 is 1.9. This I would interpret to mean that the standard carcinogen solution used by this group is almost twice as active this year as last year. It is because of data of this nature that I feel the group at Kettering must periodically redetermine their standard curve for methylcholanthrene.

Very truly yours,

/s/ R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ilk

Attachments

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Members of Committee)

MRC.54/870
CAMO.Ag.17

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

A G E N D A

for the Seventeenth Meeting to be held
at 2.30 p.m. on Friday, the 17th December, 1954
at 38, Old Queen Street, Westminster, London, S.W.1

1. Minutes of the previous meeting (MRC.54/606 - already circulated)

2. Progress Reports

   Progress Report No. XII by Dr. D. L. Woodhouse - (MRC.54/854 - CAMO 54/12) - Enclosure A

3. Plans for future research

4. Possible Carcinogenicity of Diesel Exhaust Fumes (Minute 138)

   (a) A review by Research Group No. 2 of the Institute of Petroleum - (CAMO 54/13) - to be circulated

   (b) A copy of a paper to be published in "Chemistry and Industry" by Professor G. R. Clemo - (MRC.54/856 - CAMO 54/14) - Enclosure B

5. Possible Carcinogenicity of Anti-foaming Agents

   Copies of some recent correspondence are circulated for information and discussion - (MRC.54/857 - CAMO 54/15) - Enclosure C

6. Any other business.

7. Date of next meeting.

For Specified Circulation
(Committee members only)

MRC.54/854
CAMO.54/12

Committee on the carcinogenic action of mineral oils

PROGRESS REPORT NO. XII (December, 1954)

by

D. L. Woodhouse

The experiments previously reported at 44 weeks were terminated at 52 weeks. The complete results are given in the tables, copies of which have been submitted to Dr. Irwin. These suggest that in the Rabbit Test the A series show greater activity with the exception of K_4S_2A which had 5 tumours compared with 7 tumours for K_4S_2. K_4S_6A produced the highest final number (16) cf. with 17 for the stronger standard. There seems to be a marked spread of activity over the fractions and K_4SP showed a slight activity.

No fraction showed very great activity to the mice, K_4S_8A being the most active according to the actual number of tumours produced.

The experiments on fractions produced from the picrate, and maleic anhydride treatment, and the residue materials, have now been commenced, comprising 20 fractions provided by Dr. Cruickshank and (K_4S_9) from Professor Morton.

For Specified Circulation
(Committee members only)

MRC.54/856
CAMO.54/14

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

A paper by Professor G.R. Clemo, recently
published in "Chemistry and Industry",
is circulated for information.

CARCINOGENIC ACTION OF CITY SMOKE

At Liverpool I described the isolation of fractions A, B, and C (each a mixture) from city smoke.

These have now been tested for carcinogenic action as well as 2 fractions isolated similarly from Diesel bus fumes. Fractions B and C produced malignant tumours in 12 of the 29 effective mice treated, the earliest tumour was after 6 months painting (1% - C_6H_6) but the average was 9 months. Pure 3.4 benzpyrene is recorded as producing tumours from 4 - 6 months in 50% of the mice treated. Further 13 of the mice showed skin papilloma and 5 of them lung nodules (3.4, 3.3 and 1 nodules resp.).

Fraction 'A' produced some lung nodules but otherwise has not shown the activity of B and C.

The Diesel fractions on the other hand have so far given negative results apart from one mouse developing lung nodules. It is clear city smoke has a marked carcinogenic action and that Diesel bus fumes do not appear to be an important factor in this action.

For Specified Circulation
(Committee members only)

MRC.54/857
CAMO.54/15

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

1. Copy of a letter from J.C.R. Hudson, Medical Research Council to G.H.W. Cullinan, Shell Chemicals Ltd., dated 21st October, 1954.

Re: Ministry of Housing Committee on Synthetic Detergents.

"We have heard from Professor Cruickshank, who as you know represents the Medical Research Council on this Committee, that an anti-foaming agent called 'Foamrex W' may be used in future for the prevention of foam in sewage disposal works. Professor Cruickshank tells us that this anti-foaming agent consists mainly of spindle oil and is supplied by your Company, and he has asked if one of the Council's expert committees could advise on the possible dangers that might arise from the widespread use of this substance. Accordingly I am writing to ask if you would be kind enough to let us have a detailed description of the composition of 'Foamrex W'. If at a later stage it is thought desirable to carry out some experiments on it, would it be possible for you to provide samples?"

2. Copy of reply from G.H.W. Cullinan, Shell Chemicals Ltd., dated 29th October, 1954.

"With reference to your letter of the 21st October, Foamrex W is a material imported from the States. We are, however, making available on an experimental basis at present a similar material, the composition of which is as follows:-

Spindle Oil	87.3%
Oleic Acid	10.0%
Estax 37	2.0%
Diethylene Triamine	0.7%

We believe that Estax 37 is a polyoxy-alkalene fatty acid ester. It is marketed by the Watford Chemical Co. who may be prepared to disclose to you the exact composition. It is thought that the American material, Foamrex W, is of similar constitution but using a product, Nonisol 210, in place of the Estax 37, the Nonisol being marketed by the Al Rose Chemical Co.

We shall be glad to make samples of our product available to you although we would stress that experiments now in hand may suggest modification to this formula before any product is put into larger-scale use. In particular, we are experimenting with an alternative petroleum fraction to replace the Spindle Oil."

3. Copy of Specification from Watford Chemical Co. Ltd., dated 18th November, 1954

ESTAX 37	
Main Constituent	Hexa-glycol oleate
Form	Clear yellow oily liquid
A.V.	< 5
Average Melting Point or Setting Point	< 5°C.
S.G. at 20°C.	1.01
Effect of Water, 5 gms in 45 c.c.	Forms stable creamy emulsion
Solubility (Minimum %) at 15°C. in:	
Vegetable Oil	5
Kerosene	10
Tech. White Oil	5
Type of Emulsion	Water-in Oil
Other Properties	Non-ionic

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Committee members only)

MRC.54/880
CAMO.54/17

Committee on the Carcinogenic Action of Mineral Oils

The 1953-4 Experiments with Mice

Table 1 shows the results

The Standard

The responses to D_2 were very close to those obtained in the previous year; the responses to $D(\frac{1}{2})$ were significantly greater than in the previous year. For 1952-3 the figures were:-

Standard or Fraction	E.T.L. (52 weeks)	10% Date	Total Number of Tumours
D_2	13.9 ± 0.4	11.4 ± 0.8	38
$D(\frac{1}{2})$	24.8 ± 1.6	17.1 ± 0.6	25

The relative potency of D in 1953-4 to that of D in 1952-3, using Expectation of Tumourless Life as a response, is estimated to be 1.9 with fiducial limits (P = 0.95) of 1.4 -2.8. The 10% dates give a result consistent with this but a great deal less accurate. The departure from unity is due of course to mouse variation; the result is of some interest as showing the degree of accuracy obtainable.

Fractions $K_4.4$ and $K_4.4(\frac{1}{4})$

In 1953-4, $K_4.4$ yielded two tumours and $K_4.4(\frac{1}{4})$ none. In 1952-3 neither fraction gave any tumours.

Fractions K_4S, K_4SA and K_4SP

The residue K_4SP yielded no tumours. The aromatic fractions were more carcinogenic than the non-aromatic; this shows up clearly in K_4S_8 and K_4S_8A. In the other seven pairs the differences are small, but with one exception always in the same direction. The mean difference in Expectation of Tumourless Life for the seven is 1.00 ± 0.39, which is significantly different from zero.

Table 1

Experiments with mice at Birmingham in 1953-1954.

Standard or Fraction	Expectation of Tumourless Life (limited to 52 weeks)	Date when 10% of survivors had tumours	Total number of tumours
D_2	12.9 ± 0.6	8.7 ± 0.4	40
$D(\frac{1}{2})$	18.1 ± 1.0	10.3 ± 0.6	45
$K_4.4$	50.6 ± 0.8	not reached	2
$K_4.4(\frac{1}{4})$	52	" "	0
K_4S_1	52	" "	0
K_4S_1A	50.1 ± 0.6	" "	2
K_4S_2	51.9 ± 0.2	" "	1
K_4S_2A	52	" "	0
K_4S_3	52	" "	0
K_4S_3A	51.2 ± 0.6	" "	3
K_4S_4	51.2 ± 0.6	" "	2
K_4S_4A	49.6 ± 1.3	" "	4
K_4S_5	51.2 ± 0.8	" "	1
K_4S_5A	51.2 ± 0.6	" "	2
K_4S_6	51.9 ± 0.1	" "	1
K_4S_6A	50.7 ± 1.0	46.3 ± 4.0	2
K_4S_7	52	not reached	0
K_4S_7A	50.4 ± 1.0	43.9 ± 0.6	3
K_4S_8	51.6 ± 0.4	not reached	1
K_4S_8A	47.3 ± 1.6	28.6 ± 2.3	8
K_4SP	52	not reached	0

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Committee members only)

MRC.54/875
CAMO 54/16

Committee on the Carcinogenic Action of Mineral Oils

Progress Report by W. Carruthers and J. W. Cook

We have received from Professor Morton aromatic extracts of all the sixteen 2½° distillation fractions prepared from the Kuwait crude. The top ten of these (K_4S_4Aa to K_4S_8Ab, covering the boiling range 365 - 390°C) have been subdivided into maleic anhydride extracts (M), picrate-forming parts (P) and residues (R), and suitable blends of these made up as described in CAMO 54/10 and sent to Dr. Woodhouse for the next series of biological tests. The relative amounts of the subfractions obtained from each aromatic extract, and the quantities used in preparing the blends for testing are recorded in Tables I and II. Table I also shows the amounts of maleic anhydride extracts (M) obtained from the six fractions in the boiling range 350-365° (K_4S_1Aa - K_4S_3Ab). These fractions have not yet been separated into the P and R subfractions.

Table I
Subfractions from Aromatic Extracts of Kuwait Distillates

M = Maleic anhydride extract, P = picrate-forming part, R = Residue

Fraction	b.p. of Distillate °C	Volume of "extract" received	Subfractions obtained					
			M		P		R	
			gms.	%	gms.	%	gms.	%
K_4S_1Aa	350 - 352½	530	2.6	0.90	-	-	-	-
K_4S_1Ab	352½ - 355	640	4.9	0.85	-	-	-	-
K_4S_2Aa	355 - 357½	410	3.1	0.84	-	-	-	-
K_4S_2Ab	357½ - 360	940	3.8	0.45	281	33	495	59
K_4S_3Aa	360 - 362½	1100	9.3	0.93	-	-	-	-
K_4S_3Ab	362½ - 365	1160	16.8	1.6	-	-	-	-
K_4S_4Aa	365 - 367½	570	4.4	0.86	200	39	180	34
K_4S_4Ab	367½ - 370	1130	9.7	0.95	302	30	550	54
K_4S_5Aa	370 - 372½	790	6.4	0.90	194	27	467	66
K_4S_5Ab	372½ - 375	1150	5.5	0.53	225	22	806	78
K_4S_6Aa	375 - 377½	210	1.5	0.80	98	52	83	44
K_4S_6Ab	377½ - 380	1430	11.0	0.87	243	19	942	73
K_4S_7Aa	380 - 382½	1000	9.4	1.0	280	31	420	47
K_4S_7Ab	382½ - 385	1100	10.8	1.1	280	28	640	64
K_4S_8Aa	385 - 387½	1050	8.4	0.89	207	22	546	57
K_4S_8Ab	387½ - 390	735	9.1	1.37	194	30	438	67

API 06039

Table II

Blends of Kuwait Subfractions for Biological Tests

All are to be diluted to 250 c.c. in liquid paraffin except K_4S_6Aa M, P and R, which are to be diluted to 200 c.c.

Fractions	Weight (gm.) of Subfractions in Blends		
	M	P	R
K_4S_4Aa	0.5	28	24
K_4S_4Ab	1.5	53	96
K_4S_5Aa	0.8	24	56
K_4S_5Ab	0.7	30	112
K_4S_6Aa	1.5	98	83
K_4S_6Ab	1.9	43	164
K_4S_7Aa	1.0	31	46
K_4S_7Ab	1.0	36	82
K_4S_8Aa	1.2	28	75
K_4S_8Ab	1.3	28	63

These M, P and R subfractions were prepared as outlined in previous Reports. The aromatic extract was treated with maleic anhydride at 100° for several hours, giving an acidic adduct from which after distillation over sodium hydroxide, the maleic anhydride extract (M) was recovered. The oil which had not reacted with the maleic anhydride was subsequently treated with picric acid in ethanol, when part of it separated in the form of a crystalline picrate. Decomposition of this with aklali regenerated the picrate-forming part of the oil (P). The remaining part (R) was recovered from the mother liquors of the picrate crystallisation.

We are now engaged in a detailed chemical examination of these subfractions. Three new anthracene hydrocarbons have been obtained from the maleic anhydride extracts. Fractions K_4S_1Aa M, K_4S_1Ab M and K_4S_2Aa M yielded the same colourless hydrocarbons, m.p. 223-227°, when their solutions in petroleum ether were kept at -10°. Elementary analysis of this compound indicated the molecular formula $C_{16}H_{14}$, and the ultra-violet absorption spectrum showed that it was a derivative of anthracene. Oxidation with chromic acid in acetic acid, followed by fractional crystallisation of the product afforded a quinone $C_{16}H_{14}O_2$, m.p. 241-243°, which has been identified as 2:6 - dimethylanthraquinone by mixed melting point with an authentic specimen. The melting point of 2:6 - dimethylanthracene is recorded in the literature as 250°. The hydrocarbon isolated from the oil fractions is not 2:6-dimethylanthracene but is evidently the well-known eutectic of the 2:6- and 2:7-isomers whose melting point has been given as 221-222° and 225-226°. Oxidation of the autectic produces a mixture of the corresponding dimethylanthraquinones from which in this case the 2:6-isomer was obtained. Because of the small amount of material available we were unable to isolate 2:7-dimethylanthraquinone from the oxidation product. The evidence obtained proves conclusively the presence of 2:6-dimethylanthracene in the three maleic anhydride extracts, and very strongly indicates the presence of the 2:7- isomer as well. 2:7-dimethylanthracene was previously found in the fraction K_4S_2Ab M. Two other anthracene hydrocarbons were obtained from K_4S_8Aa M and K_4S_8Ab M. One of these was a yellow hydrocarbon $C_{18}H_{18}$, m.p. 293°. The ultra-violet spectrum showed that it was an anthracene derivative, and oxidation with chromic acid yielded a quinone, m.p. 317-320°. It

has been identified as 2:3:6:7-tetramethylanthracene by mixed melting points of the hydrocarbon and of the quinone with authentic specimens. The other hydrocarbon obtained from these two fractions had m.p. 131° and also analysed for the molecular formula $C_{18}H_{18}$. Its ultra-violet absorption spectrum again confirmed the anthracene structure. The quinone $C_{18}H_{16}O_2$, obtained in the usual way, had m.p. 194-196°. The melting point of this hydrocarbon does not correspond to that recorded for any known $C_{18}H_{18}$ anthracene derivative. Further work with it is in progress. 2:3:6-trimethylanthracene, which was previously isolated from K_4S_6Ab M, has now also been found in K_4S_4Aa M, K_4S_4Ab M and K_4S_5Ab M.

By fractional crystallisation of the picrate from K_4S_6Ab P, we have isolated a hydrocarbon $C_{17}H_{16}$, m.p. 143, which has been identified as 1:2:8-trimethylphenanthrene by mixed melting point with an authentic specimen. The benzthionaphthene derivative $C_{15}H_{14}S$ from the same fraction, mentioned in the last Report, has been desulphurised with Raney nickel in boiling ethanol, thereby affording a liquid naphthalene hydrocarbon $C_{15}H_{18}$. The naphthalene structure is supported by the ultra-violet absorption spectrum which, in combination with the infra-red spectrum, suggests that it is a tri-, or possibly a tetra-, substituted naphthalene.

The present position of the chemical work might be briefly summarised as follows. There are sixteen "aromatic extracts" from all of which maleic anhydride extracts (M) and from the top ten of which picrate-forming fractions (P) and residues (R) have been prepared by the methods described above. Detailed chemical investigation has so far been largely confined to the maleic anhydride extracts (M) and even these have not yet been completely covered. Seven pure anthracene hydrocarbons have been isolated from them. The eutectic mixture of 2:6- and 2:7-dimethyl-anthracenes was found in K_4S_1Aa M, K_4S_1Ab M and K_4S_2Aa M, and 2:7-dimethylanthracene itself in the next higher fraction K_4S_2Ab M. 2:3:6-trimethylanthracene was isolated from K_4S_4Aa M, K_4S_4Ab M, K_4S_5Ab M and K_4S_6Ab M; the last of these fractions has also yielded two anthracene derivatives $C_{17}H_{16}$ of unknown structure. The first of these has m.p. 169-170°, and gives a quinone $C_{17}H_{14}O_2$ m.p. 169-170°; the other hydrocarbon melts at 224-5° and its quinone at 225-226°. Finally, as described above, 2:3:6:7-tetramethylanthracene and another $C_{18}H_{18}$ anthracene derivative, m.p. 131°, quinone m.p. 195-196°, have been obtained from K_4S_8Aa M and K_4S_8Ab M.

The two picrate-forming fractions K_4S_2Ab P and K_4S_6Ab P have yielded four homogenous compounds. From the former 1:8-dimethylphenanthrene and an unknown compound which appears from its elementary analysis and ultra-violet absorption spectrum to be a tetramethylfluorene, have been isolated. The other fraction, K_4S_6Ab P, has yielded 1:2:8-trimethylphenanthrene and a sulphur-containing compound $C_{15}H_{14}S$, known to be a derivative of 6:7-benzthionaphthene.

9th December, 1954.

ESSO LABORATORIES
STANDARD OIL DEVELOPMENT COMPANY
P. O. BOX 51, LINDEN, N.J.

MEDICAL RESEARCH DIVISION
ROBERT E. ECKARDT, PH.D., M.D
DIRECTOR
HORACE W GERARDE, PH.D., M.D.
HEAD TOXICOLOGIST

INDUSTRIAL HYGIENE SECTION
NATHAN V. HENDRICKS, CH.E.
HEAD OF SECTION
FRANKLIN W. CHURCH, M.S.
GEORGE M. WILKENING, M.S.
INDUSTRIAL HYGIENISTS

January 14, 1955

Messrs. E. W. Adams
L. C. Beard, Jr.
Allan E. Dooley
F. D. Greenway
L. K. Henderson
C. K. Kline
E. K. Linder
R. C. Mitkoff
M. M. Mosquist
James W. Osborn
F. J. Sanders

all day ?
Wednesday ?

Gentlemen:

At the January 10th meeting of the Steering Committee, it was recommended that the Subcommittee on Carcinogenicity be composed of the following people: E. W. Adams, L. C. Beard, Jr., R. E. Eckardt, C. K. Kline, E. K. Linder, R. C. Mitkoff and M. M. Mosquist, with an ex officio member, the Chairman of the Lubrication Committee, Division of Marketing. Whether or not this is now the official membership of our subcommittee, I am not sure, and therefore I am sending this letter to each of the members indicated in Mr. Stroup's memorandum of February 17, 1954.

Statler Hotel Buffalo N.Y.

I have so far heard from the following people concerning the meeting in April: Messrs. Adams, Kline, Mitkoff, Linder, Greenway, Mosquist and Beard. Of this group, four said that either April 22nd or April 23rd would be satisfactory to them. Two gave a preference for April 23rd and one gave a preference for April 22nd. As far as I personally am concerned, either day is satisfactory. Therefore, I believe that our meeting should be called for Saturday, April 23, 1955 in Buffalo. By carbon copy of this letter to Mr. Stroup, I am asking that he arrange a room for us to hold this meeting. By carbon copy of this letter to the Cincinnati group, I am informing them of the arrangements.

It is my hope to have an agenda and progress report from the Rottering Laboratory for distribution to each of you at least a week in advance of this meeting so that you will have an opportunity to read the progress report and organize your thoughts on the topics to be included in the agenda. In the meantime, I would appreciate it if each of you would let me know of any topics which you would wish to have included on the agenda of this meeting in April.

Sincerely yours,

R. E. ECKARDT, M. D.

REE:ilk

cc: Messrs. D. V. Stroup
R. A. Kehoe
J. J. Fleitz
A. Wesley Barton

API 06042

CHICAGO DAILY NEWS, Monday, Jan. 24, '55

ROADS TO DEATH?

CANCER MAY BE CAUSED BY ASPHALT, SAYS BRAZIL EXPERT

BY HENDRIK J. HERNS
Daily News Foreign Service

SAO PAULO, Brazil -- The upsurge in lung cancer may be due more to asphalt and oil than to cigaret smoking.

That is the theory advanced by Prof. Antonio Prudente, Brazil's internationally famous cancer expert.

In an exclusive interview at his cancer hospital here, Prudente, who is a pioneer in cancer surgery and hormone treatment, praised America as the leading nation in cancer research.

He also cited cortisone as one of the most effective drugs in the battle against cancer. He is now experimenting with it in leukemia cases.

PRUDENTE was one of the first to use the hormone testerone in cases of breast cancer. He experimented with it from 1939 to 1946, when the results of his studies were published in the United States.

He is also one of the few physicians in the world familiar with the adrenal operation, a type of surgery invented at the University of Chicago medical school by Dr. Charles Huggins.

HERE'S WHY HE SUSPECTS ASPHALT

Discussing the American controversy about lung cancer and cigaret smoking, Prudente told me:

--Smoking is an age-old habit, the increase of lung cancer is rather recent.

--Smoking is also a habit of people in uncivilized as well as civilized areas of the world. Yet lung cancer has increased only in the civilized areas.

--Beyond that it has increased more in countries with asphalt roads than those with concrete roads.

--Finally, it has not increased in those rural districts of the civilized world which still lack asphalt roads.

Prudente believes strongly that here lies one of the clues to the increase of lung cancer.

Nevertheless, he does not deny that tar, and thus smoking as such, may have some cancer-inducing effects. However, he believes - with German scientists, by the way - that it is not only the tobacco which may be harmful but also cigaret paper.

ONE CURE FOR ALL HELD UNLIKELY

As president of the sixth International Cancer Congress held here a few months ago, he has been and continues to be in touch with nearly every cancer expert in every part of the world.

Yet outside of minor surgical methods and a new promising Japanese drug, nitromin, he sees no indication for a quick cure for the disease.

He believes that cancer-consciousness of the public is a major tool for the cure.

It is due to this increasing consciousness that doctors today can cure most breast, stomach and skin cancers, he says.

Beyond that, he believes that science will have to find as many cancer cures as there are cancer types.

There will never be an all-embracing cancer preventive such as the Salk vaccine, which may well be the sure-fire polio preventive, he told me.

ONE OF HIS principal hopes lies in the future use of isotopes which he studies closely at the U.S. Army's atomic center in Oak Ridge, Tenn.

But he also feels that early detection is as important, if not more so, as scientific advance.

"If every doctor gave every patient that type of cancer examination that he can give in his office, we could save at least years of lives, if not the lives," he says.

from DVS for information to Members of M-A-C and staff members at Kettering Laboratory

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. BOX 51, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

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HEAD TOXICOLOGIST

BERTRAND E. BENNISON, M.D.
CHIEF CLINICAL RESEARCH PHYSICIAN

February 3, 1955

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

I am attaching recent minutes of the Committee on the Carcinogenic Action of Mineral Oil of the Medical Research Council of Great Britain. I believe that these minutes would be of general interest to the members of the Medical Advisory Committee of the API and would appreciate it if you would have them duplicated for such distribution, and also to the members of the Kettering Laboratory.

Sincerely yours,

R. E. Eckardt

R. E. ECKARDT, M. D.

REE:ilk

Encl. - MRC.55/53
CAMD.Min.17

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Committee Members)

MRC.55/ 52
CAMO.55/1

Committee on the Carcinogenic Action of Mineral Oils

The meeting of the above committee will be held at 2.30 p.m. on Monday, 2nd May, 1955, at 38, Old Queen Street, Westminster, London, S.W.1. The Agenda will be circulated in due course.

J.C.R. Hudson,
Secretary.

20th January, 1955.

MEDICAL RESEARCH COUNCIL

For Specified Circulation
(Committee members)

MRC.55/53
CAMO.Min.17

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Minutes of the Seventeenth Meeting, held at 38 Old Queen Street, London, S.W.1, on Friday, 17th December, 1954, at 2.30 p.m.

Present: Professor T. Ferguson (Chairman), Colonel S.J.M.Auld, Professor H.N. Green, Dr. T. Heiger, Dr. J.O. Irwin, Professor J.R. Squire, Dr. D.L. Woodhouse, and Mr. J.C.R. Hudson (Secretary).

Attended: Dr. W. Carruthers, (representing Dr. J.W. Cook) and Professor D. Hey.

Apologies for absence were received from: Dr. J.W. Cook and Professor F. Morton.

1. Minutes.

The minutes of the previous meeting were approved and signed.

2. Progress Reports

A. Progress Report No.XII by Dr. D.L. Woodhouse (MRC.54/854, CAMO.54/12).

It was pointed out that the standards, D and D½, were usually of about the same potency on rabbits as the fractions being tested, whereas they were more potent on mice than the oil fractions. It was therefore agreed that, in order that the standards should have approximately the same potency as the fractions under test, the standards used in future mice experiments should be D½ and a more dilute solution, say, D1/20.

B. Progress Report by Dr. W. Carruthers and Dr. J.W. Cook (MRC.54/875, CAMO.54/16).

Dr. Carruthers pointed out that the Di-methyl, tri-methyl and tetra-methyl anthracenes were being isolated from the lower medium and higher boiling fractions. This tended to confirm the effectiveness of the original distillations.

Many of the compounds which were being isolated from the various fractions were found in only milligram quantities. If, at a later stage, it was desired to test their carcinogenicity, it might be necessary to synthesise some of them in greater quantities. Professor Hey said that he already had comparatively large stocks of many of the synthetic methylated anthracenes and he would be willing to make these available if they were required.

It was pointed out that the percentage extraction of the M,P.R, subfraction given in Table I did not add up to 100%. This was due to losses in the process of separation and allowances for this had been made in calculating the blends given in Table II.

Colonel Auld asked if, in view of the spread of results amongst the fractions tested biologically, the chemists were satisfied that the methods being used could give sufficiently discreet separations. In this respect Professor Hey suggested that molecular distillation might give a better separation of small quantities.

C. Dr. Irwin's Report (MRC.54/887, CAMO.54/19).

Dr. Irwin pointed out that comparison of statistical results from year to year and between Birmingham and Leeds showed a reassuring reproducibility.

D. Professor Morton's Report.

It was noted that Lagunillas fractions were being prepared and would probably be available for biological testing to Professor Green when he was ready.

3. Possible Carcinogenicity of Diesel Exhaust Fumes (Minute 138).

The review of Research Group No.2 of the Institute of Petroleum was circulated (CAMO. 54/13).

The Secretary read a letter from Mr. E.T. Priddle offering the assistance of C.A.V. Limited in any investigation relating to Diesel exhaust fumes. In addition, Professor Hey said that a Diesel engine in the Engineering Department of King's College, London, could be made available similarly.

The Committee agreed:

(i) that in view of their own research commitments, which could be expected to last another 2 or 3 years, they could not undertake any research on this subject.

(ii) to recommend to the Council that, as the exhaust fumes from internal combustion engines are particular components of atmospheric pollution, their study might be referred by the Council to the Committee concerned with that subject, or to an ad hoc Committee; the members of this Committee specially interested in Diesel fumes would be glad to co-operate in the work so far as possible. The Chairman undertook to write to the Secretary of the Council along these lines.

4. Future Work.

Professor Green said that his biological experiments on mice and rabbits would have run for 52 weeks at the end of a further 4 weeks and 6 weeks respectively.

API 06048

(Professor Green left).

Dr. Woodhouse said that his biological experiments on mice and rabbits had been running for 6 weeks and 9 weeks respectively.

It was noted (see Minute 2, D above) that Lagunillas fractions, which Professor Morton had prepared, were ready for testing by Professor Green. It was pointed out, however, that the preliminary experiments had shown that the Lagunillas fractions were most potent above 390°C., which was beyond the limit of the Stedman still. Professor Squire undertook to ask Professor Morton to include in the batches which he sent to Professor Green a fraction or residue boiling above 390°C.
(Subsequent Note: Professor Morton proposes to obtain a Fraction 9, boiling above 390°C. by laboratory distillation of the Lagunillas residue. This will provide Professor Green with eight Lagunillas Stedman fractions and one more (L_4 S1-8 and L4.9), another nine aromatic extracts of these (L_4 S1-8A and L4.9A), and the pooled raffinate

(L4 S.R.). With the two standard solutions of 9:10 dimethyl 1:2 benzanthracene, Professor Green will thus have 21 materials for his animal tests.)

5. Possible Carcinogenicity of Anti-Foaming Agents.

The memorandum (CAMO.54/15) was received and the Secretary added that further enquiries had elicited the following additional information from Shell Chemicals Limited:

(i) that the anti-foaming agent was to be added to the sewage in the proportion of 3 parts per million;

(ii) that there was no evidence of an oil film on the surface of the settling tanks and it was therefore thought that the majority of the anti-foaming agent was carried down with the sludge.

The Committee therefore agreed:

a) that those employed at sewage works might be exposed to some hazard in handling the anti-foaming agent and that this aspect of the question might be referred to the Occupational Health Committee; and

b) that it represented a negligible hazard as far as the general population was concerned.

6. Exhaust Filters on Internal Combustion Engines.

Professor Squire mentioned that in a television programme called "Panorama" a Mr. William Wyness had demonstrated a filter for attachment to the exhausts of internal combustion engines which, it was claimed, removed particulate matter from the exhaust. The Committee agreed that this fell outside their terms of reference.

7. Conference on Atmospheric Pollution.

Colonel Auld reported that the Institute of Fuel was proposing to hold a conference on Atmospheric Pollution at the Institute of Civil Engineering on the 20th January, 1955 under the Chairmanship of Dr. Foxwell. Professor Ferguson said that he would try to attend that Conference and it was suggested that representatives of other Committees, for example the Atmospheric Pollution Committee, might also wish to attend.

8. Date of Next Meeting.

In the absence of Professors Cook, Green and Morton, it was suggested that the next meeting might be held on Monday, 18th April, Thursday, 21st or Friday, 22nd April, 1955, at 12.30 p.m. The Secretary was to ask the absent members to indicate which dates they preferred.

J. E. BUCHANAN
PRESIDENT
ARVIN S. WELLBORN
CHIEF ENGINEER & SECRETARY

H. B. PULLAR
CHAIRMAN EXECUTIVE COMM.
GEORGE R. CHRISTIE
TREASURER

PLEASE ADDRESS REPLY TO:
ASPHALT INSTITUTE BUILDING
UNIVERSITY OF MARYLAND
COLLEGE PARK, MD.

February 21, 1955

to
Mr Stoop

Mr. Frank M. Porter
President
The American Petroleum Institute
50 West 50th Street
New York 20, N. Y.

Dear Mr. Porter:

Recently I called to your attention artieles pointing the finger of suspicion at various petroleum products as possible causes of lung cancer. Supplementing that letter, I am transmitting herewith copies of press stories pertaining to the same subject.

Very truly yours,

J. E. Buchanan

J. E. Buchanan
President

JEB/h

Enc. 2

API 06050

The Louisville (Ky) Times, January 24, 1955

Expert Suspects Asphalt May Be A Major Cause In Rise of Lung Cancer

By HENDRIK J. BERNS

Special to The Chicago Daily News and The Louisville Times

Sao Paulo, Brazil, Jan. 24. — The upsurge in lung cancer may be due more to asphalt and oil than to cigarette smoking.

That is the theory advanced by Prof. Antonio Prudente, Brazil's internationally famous cancer expert.

In an interview at his cancer hospital here, Prudente told me:

1—Smoking is an age-old habit. The increase of lung cancer is rather recent.

2—Smoking is also a habit of people in civilized as well as uncivilized areas of the world. Yet lung cancer has increased only in the civilized areas.

3—Beyond that it has increased more in countries with asphalt roads than those with concrete roads.

4—Finally, it has not increased in those rural districts of the civilized world which still lack asphalt roads.

Prudente believes strongly that here lies one of the clues to the increase of lung cancer.

Also Suspects Paper

Nevertheless, he does not deny that tar and thus smoking as such may have some cancer-inducing effects. However, he believes — with German scientists, by the way — that it is not only the substance which may be harmful but also cigarette paper.

Prudente, who is a pioneer in cancer surgery and hormone treatment, praised America as the leading nation in cancer research. He also cited cortisone as one of the most effective drugs in the battle against cancer. He is now experimenting with it in leukemia cases.

Prudente was one of the first to use the hormone, testerone, in cases of breast cancer. He experimented with it from 1939 to 1945 when the results of his studies were published in the United States.

Knows Rare Operation

He is also one of the few physicians in the world familiar with the adrenal operation, a type of surgery invented at the University of Chicago Medical School by Dr. Charles Huggins.

As president of the International Cancer Congress held here a few months ago, he has been and continues to be in touch with nearly every cancer expert in every part of the world. Yet outside of minor surgical methods and a new promising Japanese drug, nitromin, he sees no indication for a quick cure-all of the disease.

However, he believes that cancer-consciousness of the public is a major tool for the cure. It is due to this increasing consciousness that doctors can today cure most breast, stomach and skin cancers, he says.

Many Cures Needed

Beyond that, he believes that science will have to find as many cancer cures as there are cancer types.

He does not believe there will ever be an all-embracing cancer preventive such as the Salk vaccine which may well be the curative polio preventive.

One of his principal hopes lies in the future usage of isotopes which he studies closely at the atomic center in Oak Ridge, Tenn.

"If every doctor gave every patient that type of cancer examination that he can give in his office, we could save at least years of lives if not the lives," he says.

Chicago Daily News, Jan 24, '55

ROADS TO DEATH

Cancer May Be Caused by Asphalt, Says Brazil Expert

BY [illegible]
Daily News Foreign Service

SAO PAULO, Brazil—The upsurge in lung cancer may be due more to asphalt and oil than to cigaret smoking.

That is the theory advanced by Prof. Antonio Prudente, Brazil's internationally famous cancer expert.

In an exclusive interview at his cancer hospital here, Prudente, who is a pioneer in cancer surgery and hormone treatment, praised America as the leading [illegible] in cancer research.

He also cited cortisone as one of the most effective drugs in the battle against cancer. He is now experimenting with it in leukemia cases.

• • •

PRUDENTE was one of the first to use the hormone [illegible] in cases of breast cancer. He experimented with it from 1939 to 1948, when the results of his studies were published in the United States.

He is also one of the few physicians in [illegible] familiar with the [illegible] operation, a type of surgery [illegible] at the University of Chicago medical school by Dr. Charles Huggins.

Here's Why He [illegible]

[illegible] the American controversy about lung cancer and cigaret smoking, Prudente [illegible]:

—Smoking is an age-old habit. The increase of lung cancer is rather recent.

—Smoking is also a habit of people in uncivilized as well as civilized areas of the world. Yet lung cancer [illegible] only in the civilized areas.

—Beyond that it has [illegible] [illegible] asphalt roads [illegible] concrete roads.

—Finally, it has [illegible] increased in those [illegible] of the civilized world [illegible] asphalt roads.

Prudente believes strongly that here lies one of the clues to the increase of lung cancer.

Nevertheless, he does not deny that tar, and thus smoking as such, may have some cancer-inducing effect. However, he believes — with German scientists, by the way — that it is not only the tobacco which may be harmful but also cigaret paper.

One Cure for All Held Unlikely

As president of the sixth International Cancer Congress held here a few months ago, he has been and continues to be in touch with nearly every cancer [illegible] in every part of the world.

Yet outside of minor surgical methods and a new [illegible] Japanese drug, nitromin, [illegible] sees no indication for a [illegible] cure for the disease.

He believes that cancer-[illegible] of the public is a [illegible] [illegible] for the cure.

It is due to this increasing [illegible] that doctors [illegible] can cure most breast, stomach and skin cancers, he [illegible].

[illegible] that, he believes that [illegible] will have to find [illegible] many [illegible] cures [illegible] [illegible] types.

There will never be an all-embracing cancer [illegible] such as the Salk vaccine, which may well be the sure-fire polio preventive, he told me.

• • •

ONE OF HIS principal hopes lies in the future use of isotopes which he studies [illegible] at the U.S. Army's atomic center in Oak Ridge, [illegible].

But he also feels that early detection is [illegible], if not more so, [illegible] scientific advances.

"If every doctor gave every patient that type of cancer examination that he can give in his office, we would save a lot of years of lives, if not the lives," he says.

API 06052

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O BOX 51, LINDEN, N. J.

MEDICAL RESEARCH DIVISION
ROBERT E ECKARDT, PH D., M D
DIRECTOR
NATHAN V HENDRICKS, CH E
HEAD INDUSTRIAL HYGIENIST
HORACE W GERARDE PH D., M D
HEAD TOXICOLOGIST
BERTRAND E BENNISON M D
CHIEF CLINICAL RESEARCH PHYSICIAN

April 11, 1955

Messrs. E. W. Adams
L. C. Beard, Jr.
Allen K. Dooley
F. D. Gassaway
L. M. Henderson
C. H. Hine
E. K. Linder
R. C. Mitkoff
M. M. Mosquist
James W. Osborn
F. J. Sanders

Gentlemen:

I thought each of you would be interested in the attached abstracts of papers to be delivered at the coming meeting of the American Association for Cancer Research. These, I believe, are the ones pertinent to us in our thinking about carcinogenicity, from the great number of papers to be delivered at that meeting.

Sincerely yours,

R. E. ECKARDT, M. D.

REE:ilk

Attachments

cc: Messrs. A. Wesley Barton
R. A. Kehoe
D. V. Streep

THE FATE OF POLYCYCLIC AROMATIC HYDROCARBONS IN SOOT FOLLOWING THEIR EMISSION INTO THE ATMOSPHERE AND DEPOSITION IN THE LUNGS

Hans L. Falk
Paul Kotin

(Univ. of Southern California School of Medicine, Los Angeles, Calif.)

The aromatic hydrocarbon content of soot-polluted atmosphere was found to differ qualitatively and quantitatively from gasoline and diesel engine exhausts. One atmospheric hydrocarbon was traced to incinerator soot and rubber tire dust.

In view of the high concentration of 3,4-benzpyrene and the absence of certain source hydrocarbons from the atmosphere, a study was undertaken to determine the fate of these compounds.

Aromatic hydrocarbons were absorbed on filter paper to determine the effects of air and light and synthetic smog upon them.

The destruction rate of these compounds varied from complete to only 20 per cent following a 48-hour exposure to air.

Synthetic smog similar to that detected in urban atmospheres attacked the hydrocarbons at varying rates. No qualitative difference was observed in the destruction of the exposed hydrocarbons either in their pure state or when adsorbed on soot. These experiments resolved the qualitative and quantitative differences in the hydrocarbons at their source and in the atmosphere.

An analysis of the lungs of the average city dweller reveals the presence of approximately 1 gm. of soot recoverable at autopsy. The soot thus obtained was measured gravimetrically. Spectrophotometric analysis of the recovered soot failed to reveal the usual aromatic hydrocarbons. The presence of the less stable carotenoids pointed to the actual absence of aromatic hydrocarbons. The absence of aromatic hydrocarbons was further substantiated by adding up to 40μg. of hydrocarbons to the extracted soot, followed by quantitative recovery of these amounts.

The rate of removal of aromatic hydrocarbons from soot deposited in the lungs of mice is now under study.

COPY/mak - 4/11/55
Proceedings of the American Association for Cancer Research
2:1, April 1955

A POSSIBLE CARCINOGENIC AGENT IN CIGARETTES

J. M. Essenberg
Aaron M. Leavitt
Edward Gaffney

(Introduced by Kurt Stern)
(Dept. of Anatomy, Chicago Medical School, Chicago, Ill.)

After completing our work on the production of lung tumors by exposure to cigarette smoke, we attempted next to discover the responsible carcinogenic agent in the cigarettes. Three possible sources were indicated; the cigarette paper, the nicotine of the tobacco, and the arsenic content of the cigarette.

Our automatic smoking machine served in all these investigations. Seventy-two A/Jax mice were used, half experimental and half controls for each experiment, with sex equally divided in each group. Each experiment lasted 1 year. Data on weight and reproductive capacity were recorded. At the end of the experiment the mice were killed, perfused, and serial sections prepared. Those that died during the experiment were similarly prepared.

Paper.--Of the 26 perfused mice exposed to the smoke from "cigarettes" made of nine sheets of cigarette paper in each, thirteen had lung tumors; eleven of the 29 controls had tumors. Hyperplasia, pneumonia, and reproduction occurred in both groups, and the weight curve of both was practically the same.

Nicotine.--Of 28 experimental mice exposed to smoke from cigarettes low in nicotine content, eighteen had lung tumors. Among 30 controls, thirteen had lung tumors. Both groups suffered from pneumonia, but only the experimental mice showed reduction in weight and inhibited reproductive capacity.

Arsenic.--0.55 Mg. of arsenic was added to the cigarettes of low nicotine content used in the nicotine experiment. The effects on the experimental animals deviated only slightly from those exposed to nicotine alone.

It is concluded that mice exposed to nicotine indicate positive results.

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2:1, April 1955

CARCINOGENIC COAL TAR DISTILLATES

William E. Poel
Adolph G. Kammer
Lloyd J. Sullivan
Charles B. Willingham
with the technical assistance of Mary C. Stezoski

(Introduced by Robert E. Olson)
(Graduate School of Public Health, Univ. of Pittsburgh, and the Mellon Inst., Pittsburgh, Pa.)

The recognition of 3,4-benzpyrene as a coal-distillation by-product led some investigators to assume that it is the most potent, if not the only, carcinogen in tar or pitch. This assumption is not supported by findings published during the past decade and data developed in our laboratory during the past 2 years. Commercially available coal distillates containing no demonstrated amounts of benzpyrene have been found to possess tumor-inducing potency comparable with that of our standard solutions of 3,4-benzpyrene.

Distallates were tested from by-product coke ovens of the type used to carbonize more than 90 per cent of the coal coked in the United States in normal times. Solutions of the test materials in benzene or toluene were applied to the shaved, interscapular areas of C57/BL/6 mice 3 times weekly until a malignant papilloma developed or the animal died.

Crude tar and the pitch residuum of the tar after fractional distillation were bioassayed in this manner and found to possess carcinogenic activity comparable with that reported in literature for tars and pitches distilled industrially under conditions not necessarily identical with those used by our sources. Among the intermediate fractions tested and found to be actively carcinogenic were two grades of creosote oil, and a "crystal-free anthracene oil" widely used as a wood preservative. A technic of chromatographic separation and spectroscopic analysis believed to be capable of identifying 3,4-benzpyrene in concentration of 0.005 per cent has thus far failed to reveal this substance in the oils tested. Creosote oil has been reported in the literature to possess co-carcinogenic and anticarcinogenic components, but the oil itself apparently has not previously been reported as being carcinogenic. Preliminary data on the carcinogenic activity of the fractional distillates ranging from tar through pitch will be presented and discussed.

The authors have had no opportunity to search for human case experiences related to the industrial use of the materials tested, and would discourage inferences from animal data alone that substances are carcinogenic for humans.

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2:1, April 1955

THE EFFECTS OF VERY LOW CONCENTRATIONS OF CARCINOGENS IN EPIDERMAL CARCINOGENESIS: A COMPARISON WITH CO-CARCINOGENS

Philippe Shubik
Umberto Saffiotti

(The Chicago Medical School, Div. of Oncology, 2755 W. 15th St., Chicago, Ill.)

A study of the action of very low concentrations of carcinogen on the skin was made in order to analyze: (a) the production of tumors with a solution containing "traces" of carcinogen, comparable to impurities in certain industrial products; (b) the effect of the same solution when used as a promoting agent.

A group of 30 Swiss female mice was painted once with a single application of 1.0 per cent 9,10-dimethyl-1,2-benzanthracene in mineral oil and then repeatedly with a 0.01 per cent solution of the same carcinogen. Another similar group received only repeated paintings with the 0.01 per cent solution.

The yield and progression of the induced tumors were analyzed. The pretreatment with a single application of a 1.0 per cent solution, insufficient to produce tumors unaided, shortened the latent period for the appearance of the tumors brought out by the repeated applications of the 0.01 per cent solution; the pattern of tumor induction seemed similar in the two groups but differed substantially from that of mice treated with a single application of carcinogen followed by the promoting agent croton oil. This again emphasises the specificity of action of croton oil and distinguishes it clearly from activity that might be attributable to weak carcinogenic action.

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2:1, April 1955

FRACTIONATION OF CIGARETTE TAR

George F. Wright
Ernest L. Wynder

(Dept. of Chemistry, Univ. of Toronto, Toronto, Canada, and
the Section of Epidemiology, Sloan-Kettering Inst. for Cancer Research, New York, N.Y.)

The present research program attempts to identify the agent or agents responsible for the established carcinogenic activity of cigarette tar to mouse epidermis.

Tar has been examined from smoked whole cigarettes as well as those which have been extracted with chloroform prior to smoking. The cigarette tar is separated into 10-15 per cent bases, 12-18 per cent acids, and 50-60 per cent neutral material, all chloroform-soluble. The remainder is water-soluble.

The narcotic part of the basic tar, comprising 47 per cent of the total bases, is removed in order that test animals can survive.

The acidic part of the tar has yielded a highly fluorescent compound, $C_{12}H_{12}O_5$.

The neutral fraction, which still contains over 1 per cent of nitrogen, has been separated by molecular distillation as well as by bulk elution from silica gel with successive solvents of increasing polarity. Fraction 1 (no N) principally contains saturated hydrocarbons. Fraction 2 (0.36 per cent N) contains highly fluorescent material, the ultraviolet spectrum of which resembles that of compounds like 3,4-benzpyrene. This spectrum is enhanced by deliberately adding 3,4-benzpyrene prior to chromatography. It is estimated that not more than about 1 part per million of 3,4-benzpyrene can be present in the total tar. Fraction 3 (0.6 per cent N) and especially Fraction 4 (1.5 per cent N) yield a crytalline compound (m.p., 86° C.), comprising 0.01 per cent of the total tar. The greater part of the nitrogenous material is found in Fractions 5 and 6 (4-6 per cent N).

All the fractions are applied to CAF_1 and Swiss mice. The chloroform-insoluble, the basic-free, the acidic, the basic (nicotine-free), and neutral tars are applied in 50 per cent concentration; and the molecular distillates and the chromatographic eluents of the neutral tar, in 10 per cent solution. We feel that as yet unestablished carcinogens or co-carcinogens are in tobacco tar, since the concentration in which benzpyrene seems to be in cigarette tar is insufficient to account for the observed carcinogenic activity to mouse epidermis.

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2:1, April 1955

FURTHER PRODUCTION OF CARCINOMA WITH CIGARETTE TAR

Ernest L. Wynder
Evarts A. Graham
Adele B. Croninger

(Dept. of Surgery, Washington Univ. School of Medicine, St. Louis, Missouri, and the Section of Epidemiology, Sloan-Kettering Inst. for Cancer Research, New York, N.Y.)

Tests on different mouse strains.--Swiss and C57 mice were painted with cigarette tar in a manner similar to that reported for CAF_1 mice, with the exception that the tar had been standing in acetone longer than in the previous experiment.

Among Swiss mice 22 papillomas and twelve cancers were noted among 86 mice. The respective results for C57 mice were ten papillomas and two cancers among 89 mice, whereas those previously reported for CAF_1 mice were 48 and 36 out of 81 mice.

The data show Swiss mice to be a more susceptible strain to cigarette tar painting than C57 mice.

The possibility is advanced that the higher rate of lesions in CAF_1 mice could be because this experiment was conducted with tar that was fresher than that used in the second experiment. Possible chemical alterations of the tar as a consequence of standing in acetone solution, which could lead to a decrease of carcinogenicity, are discussed. The observed differences may also be due to differences in strain susceptibility.

It is suggested that in experiments using cigarette tar as a possible carcinogen the tar be prepared freshly once a month, be refrigerated in brown bottles, and that the acetone solutions used for the applications be prepared at bi-weekly intervals.

Tests with denicotinized cigarette tar.--CAF_1 mice were painted with a cigarette tar from which nicotine had been removed by washing the tar with a 2 per cent solution of HCl. Up to date the animals had been painted for 13 months. Papilloma and carcinoma formation is so far somewhat greater than observed with total tobacco tar. This may be due to the fact that the animals were able to tolerate denicotinized tar better. These data suggest that there are mouse carcinogens in tobacco independent from any that might be present in the basic fraction.

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Proceedings of the American Association for Cancer Research
2:1, April 1955

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O. BOX 51, LINDEN, N. J.

MEDICAL RESEARCH DIVISION
ROBERT E ECKARDT, PH.D., M.D.
DIRECTOR
NATHAN V HENDRICKS, CH.E
HEAD INDUSTRIAL HYGIENIST
HORACE W GERARDE, PH D., M.D.
HEAD TOXICOLOGIST
BERTRAND E BENNISON, M.D.
CHIEF CLINICAL RESEARCH PHYSICIAN

April 12, 1955

Dr. E. W. Adams
Dr. L. C. Beard, Jr.
Mr. Allan E. Dooley
Dr. F. D. Gassaway
Dr. C. H. Hine
Dr. E. K. Linder
Dr. M. M. Marisic
Dr. R. C. Mithoff
Dr. M. N. Newquist
Dr. James W. Osborn
Dr. F. J. Sanders

Gentlemen:

Attached is the agenda for the meeting of the Subcommittee on Carcinogenicity of the API Medical Advisory Committee to be held on Saturday, April 23, 1955 at the Hotel Statler in Buffalo.

Sincerely yours,

R E Eckardt

R. E. ECKARDT, M. D.

RKE/mak
Att.

cc: Mr. D. V. Stroop ✓
Dr. A. W. Horton
Dr. R. A. Kehoe
Dr. J. Phair

AGENDA FOR THE MEETING OF THE SUBCOMMITTEE ON CARCINOGENICITY
OF THE API MEDICAL ADVISORY COMMITTEE

Saturday, April 23, 1955

Detroit Room, Hotel Statler, Buffalo

9:30-10:30 a.m. - Executive Session - Subcommittee Members Only

10:30 a.m. - Subcommittee Meeting - Medical Advisory Committee Members and Guests Welcome

I. Approval of Minutes of Previous Meeting

II. Progress Report by Dr. A. W. Horton

III. Progress Report by Dr. J. Phair

IV. Comments, if any, by Dr. R. A. Kehoe

V. Efficiency of Solvent Extraction in Removing Carcinogens from Lubricating Oils

VI. Emulsion Techniques

VII. Possible Lung Carcinogenicity of Lubricating Oil Mists

VIII. Any Other New Business

IX. Executive Session if Necessary

X. Adjournment

THE STANDARD OIL COMPANY

April 15, 1955

Dr. R. E. Eckardt, Director
Medical Research Division
Esso Research & Engineering Co.
P.O. Box 51
Linden, New Jersey

Re: OCCUPATIONAL CANCER HAZARDS
by W. C. Hueper, M.D.

Dear Dr. Eckardt:

In reference to our recent correspondence regarding the above subject and our telephone conversation of today, I am enclosing two (2) copies of this article by Dr. Hueper distributed March 9, 1955 to members of the NPA Fire and Accident Prevention Department by E. H. Fallin of the National Petroleum Association in Washington.

Very truly yours,

J. W. Osborn, M.D.

JWO:amd
Enc. (2)

CC: Dr. George M. Saunders
Mr. D. V. Streep

OCCUPATIONAL CANCER HAZARDS

by
W. C. Hueper, M.D., National Cancer Institute

(The article reprinted herewith was prepared for the March-April, 1955 issue of "Safety Standards" a publication of the U. S. Department of Labor.)

The rapid development of modern industrialism has been associated with the appearance of many new occupational health hazards of which those causing cancers occupy an important position.

The term "occupational cancer" is applied to malignant tumors originating in individuals during the course, and/or as the result of the regular and usually prolonged exercise of certain occupational activities entailing contact with some exogenous, physical, chemical or parasitic agent acting in proper intensity. Occupational cancers thus are caused by specific agents or etiologically related to well-defined occupational conditions which form an integral part of the ordinary working environment. They differ through these aspects from the accidental occupational cancers which result from or follow upon some extraordinary, unforeseen, accidental injury sustained at work and being of a nonspecific nature.

Types and Nature of Occupational Carcinogens

Occupational agents which are known or strongly suspected as having caused cancers of various organs in workers who became exposed to them are largely chemicals. Some of these chemicals are well defined (arsenicals, chromium compounds, nickel, asbestos, benzidine, beta-naphthylamine, 4-aminodiphenyl, benzol), others consist of variable mixtures of a large number of chemical compounds, a few of which possess carcinogenic properties and some of which have been identified (soot, coal tar, pitch, bitumen, tar oils, creosote oil, anthracine oil, lamp black, lignite tar and crude paraffin oil; shale oil and various petroleum fractions (industrial fuel oils, diesel oils, lubricating oils, cutting oils, crude paraffin oils, petroleum tars, pitches, asphalt and coke), and crude isopropyl liquor produced in the manufacture of isopropyl alcohol).

A second group of occupational carcinogens is composed of agents characterized by their ionizing and nonionizing radiation (x-radiation, radioactive substances, ultraviolet radiation). The third group is represented by environmental agents and conditions which sometimes have an occupational association, and which may be related to certain infections (schistosoma hematobium) or several specific climatic, geologic, dietary, and nutritional conditions, and which in part have a more or less indirect relation to carcinogenesis (malnutrition with protein and vitamin B-complex deficiency).

In addition to these established occupational carcinogens there are a number of potential human carcinogens which have been shown to elicit cancers in experimental animals and to which workers become exposed during their regular occupational activities (synthetic estrogens, chlorinated aliphatic hydrocarbons, methylated naphthalenes, diethylene glycol, p-thiourea, thio-acetamide, light green SF, brilliant blue FCF, fast green FCF, butter yellow, beryllium, selenium, cobalt, and various polymerized plastics). These potential agents also must be considered in the adjudication of compensation claims.

Evaluation of Evidence

For the establishment of casual relations between an exposure to these agents and the subsequent development of a cancer of an occupational genesis and therefore compensable nature, the following prerequisites must be fulfilled.

NATIONAL PETROLEUM ASSOCIATION

F&S 55-3

MUNSEY BUILDING • WASHINGTON 4, D. C.

METROPOLITAN 8-3722

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TECHNICAL AND SAFETY DIRECTOR

HORACE L. LOHNES
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COMMERCE COUNSEL

H. A. MILLER
EXECUTIVE ASSISTANT

March 9, 1955

TO: MEMBERS NPA FIRE AND ACCIDENT PREVENTION DEPARTMENT

In comparatively recent years, cancer hazards in industry have been recognized as of increasing importance and magnitude. Several organizations are devoting considerable study to the problem and health authorities in many large cities are watching the situation very closely in the areas of their jurisdiction so that necessary rules and regulations may be enacted if, in their opinion, they become necessary for the safety of workers.

Because certain petroleum products or materials produced in the refining of crude oil are among those listed as occupational carcinogens, a recent article appearing in the March-April, 1955 issue of "Safety Standards" a booklet published by the Bureau of Labor Standards of the United States Department of Labor, should be of particular interest to all those concerned with the protection and safety of workers. The article referred to in "Safety Standards" titled, "Occupational Cancer Hazards" by Dr. W. C. Hueper, M.D. of the National Cancer Institute, is, in our opinion, of sufficient importance for us to reproduce it for your information and file. A copy of Dr. Hueper's article as it appeared in "Safety Standards" is attached hereto.

E. H. FALLIN

API 06064

a. Definite evidence must be available indicating that the claimant had occupational contact with any one of the various agents listed; that this contact was either of prolonged nature extending as a rule over periods of at least 6 months; and was of adequate intensity for eliciting a cancerous response, according to any previous experience which might be available on this point. Single exposures may be considered to be effective if the causal agent consists of external ionizing radiation or the exposure mechanism favors the production of a carcinogenic depot in the tissues from which a prolonged exposure of the host organism may ensue.

b. The route of exposure to or introduction of the carcinogenic agent in addition to its specific chemical properties and metabolic peculiarities determine the site of the organ or tissues in which a cancer is elicited. Therefore, not any cancer, but only cancers of specific sites are related to any particular carcinogenic agent.

c. The type of exposure does not need to be continuous or extend up to the time of appearance of the cancer, but may be intermittent. In fact, any contact with the occupational carcinogenic agent may have ceased many months to years, or occasionally, even decades before the cancer becomes manifest. Effective carcinogenic exposures may be sustained not only by the ordinary operators employed in operations with occupational carcinogenic hazards, but also by workers entering such operations on a transitory basis, such as supervisors, maintenance personnel, repairmen, truckers, loaders, yardmen, and workers employed in rooms and buildings near the hazardous operations, if housekeeping and exhaust disposal methods are inadequate and environmental contaminations result.

d. Occupational Medical Stigmata--For the establishment of causal relations between occupational exposures to carcinogens and subsequently appearing cancers, it is of distinct value to analyze the medical history of affected persons for functional or anatomic disease manifestations characteristic of a pathogenic action of the particular carcinogen allegedly involved. Such noncancerous and often preparatory or precancerous symtoms of etiologic specificity act as stigmata or biologic fingerprints supporting not only the actuality of a previously sustained specific exposure, but also its causal relationship to the cancer present. Symptomatic manifestations possessing such a significance are, for instance, chronic radiodermatitis, chronic tar dermatitis, arsenic dermatosis, chronic solar dermatitis, chronic radiation periostitis, asbestosis of the lung and leukemoid reactions after exposure to benzol and ionizing radiation. Chemical analyses of tissues for the incriminated chemical also may sometimes help in establishing previous contact with any specific occupational carcinogens, such as arsenic, chromium, nickel, radioactive substances, and benzol.

It is important, however, to note that these procedures are not applicable for all occupational cancers. Some carcinogens do not produce any etiologically characteristic symptoms; in fact, they may not elicit any preliminary toxic or other disease phenomena despite a persistent and prolonged carcinogenic exposure. Thus, cancers of the bladder in dye and rubber workers may develop in the absence of any preliminary local or general warning symptoms after more than one or two decades of continuous, intermittent, or discontinued exposure to certain carcinogenic aromatic amines.

There also does not exist any parallelism between the toxic and/or irritative properties of any chemical and its potential carcinogenic qualities, nor, is there a relationship between the degree of toxicity of any particular carcinogen and its relative carcinogenic potency.

e. Extensive experience with occupational cancers indicates that there usually elapses a latent period of years, if not decades, between the onset of exposures to a carcinogenic agent and the appearance of the resulting cancer. It is for this reason most unlikely that occupational cancers become manifest within the first year following the inception of contact with a carcinogenic agent. In fact, all cancers which make their appearance during the first three years of occupation in a carcinogenic environment should be subjected to severe scrutiny for a more probable nonoccupational origin before they may be considered from an occupational viewpoint.

Compensation Laws

Workmen's compensation laws enacted in various countries and states reveal a remarkable lack of uniformity as to the types of occupational carcinogenic agents, industrial operations with carcinogenic hazards, and occupational cancers covered. As of October 1, 1954, full coverage laws applying to all kinds of occupational diseases including cancers had been passed in 26 States in the United States and the District of Columbia; schedule coverage laws not always covering occupational cancers, or all types, were in force in 20 States and no occupational disease laws had been enacted at that time in 2 States (Mississippi and Wyoming).

While workmen's compensation laws based on the principle of schedule coverage may provide some degree of compensation against disability and injuries resulting from occupational cancer hazards, such legal provisions designed for the protection of workers are totally inadequate, if not obsolete, in an era of rapidly changing and increasing occupational disease panorama.

However, even the blanket or general coverage compensation law which is sufficiently flexible to include not only the present but also any future occupational cancer hazards, usually has a statute of limitations which is inadequate for providing fair protection under certain and not too unusual circumstances met with in occupational cancers. Since occupational cancers may become manifest many years after cessation of exposure to occupational carcinogenic agents, a statutory time clause of from six months to six years may be too short for occupational cancers which may appear after a longer period.

In the workmen's compensation laws existing in most States, certain groups of workers or employees, such as especially farm labor and domestic servants, are excluded from coverage by the law. Since farming as well as housework have become and are increasingly becoming occupations having extensive contact with industrial products (pesticides, herbicides, synthetic fertilizers, antisprouting agents, hormonal fattening agents of livestock, lubricants and fuel of farm machinery, residual oils for smudge pots, soil improvers, antibiotics, detergents, waxes, polishes, dry cleaning agents), there is no sound scientific reason for excluding members of such occupations from coverage by the workmen's compensation laws and from adequate protection against cancers arising from exposure to potential and actual occupational carcinogens.

Labor Codes and Standards

Any attempt toward achieving an adequate compensation by financial means for a cancerous condition acquired through contact with occupational agents not only presents considerable economic difficulties but is also of questionable humane merit. While such a procedure is evidently the best that can be done after an occupational cancer has become an accomplished fact, the wiser, more rational, and in the long run, more economical approach to a reasonable control of occupational cancer hazards lies obviously in their prevention wherever this is possible.

The goal can be achieved to a large degree by the enforcement of proper work conditions in operations in which cancer hazards exist, so that either any contact of workers with such agents is eliminated or reduced to an ineffective level. As to the fundamental step for accomplishing such a control of occupational cancer hazards, it would be advisable to have all factories, workshops, laboratories and other establishments producing, handling, or using known or suspected carcinogenic materials to register with the appropriate State public agency. This information would provide the basis for establishing the supervision of plants by health or labor agencies and would create the proper machinery for familiarizing managers of such operations with the potential carcinogenic properties of the substances and devices used in their establishments and with the methods and procedures by which they might be controlled or avoided.

The relative effectiveness of any medical, sanitary and technologic control measures to be adopted can best be determined by ascertaining the changes in the occupational cancer incidence among the total population at risk occurring during some 10 to 30 years after their introduction. It is therefore desirable that provisions be made for routinely recording all cancer cases occurring among worker groups exposed to occupational carcinogens. All precancerous and cancerous lesions observed among members of such groups should for this reason be made notifiable with the State health agency. All persons having knowledge of these cancers should be held responsible for such reporting. The adoption of such measures represents an important step from a public-health viewpoint, because there is a growing urgency to determine the environmental causes responsible for significant changes in the incidence rates of several cancers.

What, Then, Are the Conclusions?

1. The increasing rate at which occupational carcinogens have been discovered during recent decades suggests that only a fraction of the actually existing industrial carcinogens are known and that heretofore unknown and new occupational carcinogens may be added to the present industrial environment through the development and use of new chemicals and production methods.

2. There is a great deal of evidence indicating that only a relatively small fraction of the cancers produced through contact with occupational carcinogens has been recognized and/or placed on record. Because of the established widespread industrial contact of large worker groups with known occupational carcinogens, the potential scope of the occupational cancer problem evidently is much larger than apparent from the reported number of occupational cancer cases and hazardous industrial operations.

3. Medicolegal decisions in compensation procedures of occupational cancer claims should be based on a competent and critical evaluation of the entire evidence related to the exposure conditions of the claimant, the presence or absence and the type of any symptomatic manifestations observed during the latent and developmental periods of the cancer and characteristic for a particular agent, the length of the latent period, the site of the cancer, any specific histologic and histochemical characteristics, the production of corresponding cancers in experimental animals by the incriminated agent and pertinent epidemiologic data.

4. Schedule coverage laws are inadequate for providing proper protection against occupational cancer hazards because of the dynamic state of modern industry resulting in the constant addition of new chemicals and production methods which may entail heretofore unknown occupational cancer hazards. The statute of limitations contained in the general coverage laws represents its main defect in the fair and equitable application of this type of workmen's compensation law to occupational cancer hazards.

5. Since the prevention of occupational cancer hazards and not financial compensation for established occupational cancers appears to be the more sensible and humane method of control, labor codes should be properly adjusted and enforced so as to eliminate or reasonably contain occupational cancer hazards in modern industries.

6. For ascertaining the actual scope of the occupational cancer problem and for the institution of adequate control measures, it is essential that occupational cancers and precancerous conditions are made notifiable with local and State health and labor authorities.

7. A comprehensive study of occupational cancer hazards will provide a sound basis for an equally urgent investigation of the apparent extension of industry-related cancer hazards to large parts of the general population.

UNIVERSITY OF CINCINNATI
DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH

THE KETTERING LABORATORY
COLLEGE OF MEDICINE—EDEN AVENUE
CINCINNATI 19, OHIO

CABLE ADDRESS: KETLAB, CINCINNATI
TELEPHONE: CAPITOL 5414

May 3, 1955

Mr. D. V. Stroop
Director, Dept. of Technical Services
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Dave:

Enclosed is the original copy of my report which I trust will permit you to make a satisfactory stencil. This is going to save us a great deal of work.

A separate letter is going out to each Medical Director, giving them their identifying number for their company so they can interpret the attached table.

It was very nice to see you for a moment in Buffalo. and I hope we can get together for a longer period sometime in the future.

With very best personal regards, I am

Sincerely yours,

John J. Phair, M.D.

Enclosure

cc: Dr. Robert E. Eckardt

Copy from D. V. Stroop for information of Members of Medical Advisory Committee
May 6, 1955

API 06068

Subcommittee on Carcinogenicity
API Medical Advisory Committee

Epidemiological Studies
Kettering Laboratory

Buffalo, New York
April 23, 1955

I. Central Registration

No tabulations of the newly reported cases have been prepared for review at this time. This does not imply that progress has not been made during the past year, but is due rather to the extensive changes in our methods of handling the reports. As noted at the last meeting of this Subcommittee, use of the Key Sort Cards (hand tabulation) was discontinued and IBM equipment (electronic tabulation) substituted.

This action was taken in order to obtain greater flexibility and to permit the study of more variables with less effort. However, it did require the preparation of an entirely new code since more items in some detail were included; clerks had to be trained to code and punch; and the necessary basic equipment had to be assembled. These activities are still in progress.

Although additional clerical assistants were assigned to this particular project, much more time will be necessary before the change-over is completed. To date only some 17% of the more than 1800 records now on file have been recoded. It is anticipated, however, that the staff engaged in this effort can be further augmented this summer.

During this period the number of cases reported to the Central Registry also has increased significantly. Over 500 new records have been received since January 1, 1954, the date of the last complete report. Two more companies have begun to send in their records, and the others generally are making every effort to keep up with their current cases. A table is appended giving the number of cases reported each year since the establishment of the registry. (The participating companies have been given a code number, but each will be notified separately how to identify their record.)

Geographical coverage of the industry is now almost complete. Efforts in the future will be directed to improve the accuracy of the reporting and to include a larger number of employees in the reporting base. Some participating companies are represented by a single refinery. It can be anticipated, however, if this progress is maintained, that significant figures soon will be forthcoming.

II. Special Studies

At the 1954 meeting, it was pointed out that central registration of cases, although very useful from many aspects, could not be considered an epidemiological study. From the very beginning of the project, a search has been underway to find other avenues to explore. These included health examinations, insurance statistics, and similar records.

Last year, two companies were found to have certain records deemed worthy of review with the thought of arranging for more detailed investigations. This has been done, and, unfortunately, it must be reported that for the time being these records are not in such a form as to permit valid or useful studies. However, this approach should not be abandoned, and it is proposed that the search will continue for a feasible method of employing routine medical or insurance records in the solution of this problem.

At this point it seems desirable to call attention to a proposed mortality study devised for the coal tar industry. Central registration, patterned after the API mechanism, has already been established. However, due to entirely different personnel practices and production methods, it is believed that a valid study of causes of death as related to exposure to coal tar and fumes might be feasible.

An outline of the suggested approach is attached to this report. It will be noted that the experience of high and low level exposure employee groups is to be compared using not only company records but also information obtained from Social Security files and health department records. This is considered essentially a pilot study, but, if successful, this technique could be adapted to other similar situations.

Enclosures

Total Number of Cases Received From API Member Companies

As of April 26, 1955

Company Number	1950	1951	1952	1953	1954	1955
1	-	-	-	-	-	-
2	5	-	-	-	-	-
3	-	-	-	-	-	-
4	-	-	-	-	-	-
5	-	-	-	-	-	-
6	-	233	37	-	-	-
7	-	60	-	22	16	7
8	-	88	6	-	-	-
9	-	-	-	-	73	-
10	-	-	-	-	10	4
11	-	-	26	-	-	-
12	-	1	9	11	14	11
13	-	-	-	-	-	-
14	-	7	20	12	26	3
15	-	6	4	3	12	3
16	-	-	-	-	-	-
17	-	64	10	53	29	30
18	-	-	-	141	59	20
19	-	35	21	17	12	4
20	-	-	-	-	-	-
21	-	-	-	-	-	-
22	-	-	-	-	-	-
23	-	236	-	53	44	1
24	-	-	-	-	-	102
25	-	126	7	2	25	19
Total per year	5	856	140	314	320	204

Total number of cases reported by April 26, 1955 - 1839

Kettering Laboratory
Department of Preventive Medicine & Industrial Health
College of Medicine
Cincinnati, Ohio

Coal Tar Project

Proposed Mortality Study

I. Objective

To compare mortality rates of certain groups of employees of the sponsoring companies for

(1) cancer of various sites but with particular interest in pulmonary neoplasms and

(2) other important causes of death including those usually considered degenerative.

The comparisons will take into account the

(1) occupation of the workers by broad categories determined essentially by degree of pulmonary exposure to tar fumes,

(2) length of employment by the sponsoring companies and

(3) other variables if they prove important.

II. Population Sample to be Studied

It will be necessary to have at least 2,500 essentially unselected employee records furnishing approximately 25,000 person years of experience in the coke and tar distillation plants to test this approach. Even with a sample of this size, negative findings cannot be relied upon although positive results would be significant. The workers to be accepted for inclusion in the study sample will be:

(1) All employees and pensioneers on the rolls of the coke or tar distillation plants of the participating companies in the year 1940 who had had at least five years service in such operations.

(2) All employees of the coke or tar distillation plants who complete five years service in such operations during the subsequent decade ending January 1, 1951.

III. Information to be Collected

(1) Plant Identification
(2) Employees Initials
(3) Identifying Code Number
(4) Social Security Number
(5) Year of birth
(6) Race
(7) Veteran Status (if available)
(8) Army Serial Number (if available)
(9) Occupational History
(10) Present Work Status
(11) Year employed by the reporting company
(12) Year of employment termination regardless of cause
*(13) Year of death (if available)
*(14) Cause of death (if available)
*(15) Place of death (if available)

If the starred items (numbers 13, 14, and 15) are unobtainable from company files, an attempt will be made to complete the record by a search of Social Security and Health Department files. It is hoped that this maneuver will reduce the error created by loss of individuals from the study universe due to changes in employment, residence, and other factors.

IV. Methods

(1) A standard form will be prepared to collect the desired information.
(2) The participating companies will complete the record for such employees that fall into the categories described under II. The use of an identifying code number and initials of the individual employee will protect his identity and take care of company liability.
(3) The information so collected will be transferred to IBM cards for electronic tabulation.
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cc: Dr. Robert E. Eckardt

Copy from D. V. Stroop for information of
Members of Medical Advisory Committee
May [illegible]

API 06074

Subcommittee on Carcinogenicity
API Medical Advisory Committee

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Kettering Laboratory

Buffalo, New York
April 23, 1955

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16	-	-	-	-	-	-
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18	-	-	-	141	59	20
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THE ATLANTIC REFINING COMPANY
INCORPORATED - 1870
PETROLEUM PRODUCTS
260 SOUTH BROAD STREET
PHILADELPHIA 1, PA.

INDUSTRIAL RELATIONS DEPARTMENT
E. KERN LINDER M.D. DIRECTOR MEDICAL DIVISION

June 13, 1955

R. R. Rukert, M. D.
Medical Research Division
Esso Research & Engineering Company
P. O. Box 51
Linden, New Jersey

Dear Bob:

As a member of the Subcommittee on Carcinogenicity, I would be in favor of making a recommendation to the Medical Advisory Committee that we support Dr. Bowman's research, starting this September if possible, and include in that recommendation a continuation of study for a second year for another $3000.

By that time we should have a fair appreciation of the value of this work and if it should be continued.

Sincerely,

E. KERN LINDER, M. D.

EKL:mb
cc: Dr. E. W. Adams
Mr. D. V. Stroop

IBM Card Code

API Project

February 1, 1955

Column

Case Number - Punch directly

1-3

MEMORANDUM

Column 1 - Hundreds
Column 2 - Tens
Column 3 - Digets

September 3, 1955

To: Members of the Subcommittee on Carcinogenicity, Medical Advisory Committee of the American Petroleum Institute

Year of Injury

X - Prior to 1950
Y - As a double punch - 1960 and over
0 - 1950
1 - 1951
2 - 1952

From: John J. Phair, M.D., The Kettering Laboratory

1. The information collected during the past several years by The Kettering Laboratory from the various participating companies has now been transposed to IBM cards. Enclosed is a copy of the code which was prepared for this maneuver.

2. With electronic sorting many more tabulations in a greater detail can be readily prepared. We are planning sorts following the pattern that was established in earlier reports, and we hope to submit some of these earlier tabulations.

3. However, while this work is in progress, it seems desirable to ask the members of the Sub-committee for any suggestions that they might have for additional tabulations. It may not be possible to do these in time for the November meeting, but we will be happy to have ideas from you to guide our efforts in the future. The enclosed code will indicate the kinds of breakdowns which are now feasible.

*X3 - North Eastern - Central States:

Arkansas Louisiana

5 - South Pacific States:

California

*X5 - North Pacific States:

Oregon Washington

6 - Marine Workers (Crews and Terminal Employees)
7 - Pipe Line Crew and Production Workers
8 - Outside USA

John J. Phair, M.D.

Enclosure

API 06081

IBM Card Code

API Project

February 1, 1955

Column

1-2-3 **Case Number** - Punch directly

Column 1 - Hundreds 001
Column 2 - Tens
Column 3 - Digets

4 **Year of Report**

X - Prior to 1950
Y - As a double punch - 1960 and over
0 - 1950
1 - 1951
2 - 1952
3 - 1953
4 - 1954
5 - 1955
6 - 1956
7 - 1957
8 - 1958
9 - 1959

Column

7 (Note double * punching) Geographic Location (Residence or place of employment at time of report)

0 - Not Specified - Unknown
1 - North Eastern States:

Connecticut	New Jersey
Delaware	New York
Illinois	Ohio
Indiana	Pennsylvania
Kentucky	Rhode Island
Maine	Vermont
Maryland	Virginia
Massachusetts	West Virginia
Michigan	Wisconsin
New Hampshire	

2 - South Eastern States:

Alabama	North Carolina
Florida	South Carolina
Georgia	Tennessee
Mississippi	

3 - North Central States:

Colorado	North Dakota
Idaho	South Dakota
Kansas	Utah
Montana	Wyoming
Nebraska	

*X3 - North Eastern - Central States:

Iowa	Missouri
Minnesota	

4 - South Central States:

Arizona	Oklahoma
New Mexico	Texas

*X4 - South Eastern - Central States:

Arkansas	Louisiana

5 - South Pacific States:

California	Nevada

*X5 - North Pacific States:

Oregon	Washington

6 - Marine Workers (Crews and Terminal Employees)
7 - Pipe Line Crew and Production Workers
8 - Outside USA

Sex and Race

0 - Unknown or not given
1 - Male, white
2 - Male, colored
3 - Male, other races
4 - Male, race unknown
5 - Female, white
6 - Female, colored
7 - Female, other races
8 - Female, race unknown

Work Status at Time of Report

0 - Unknown or not given
1 - Active
2 - Leave
3 - Retired
4 - Other

Age on Date of Report

X - Under 30 years
Y - Dead
0 - Unknown or not given
1 - 30-34
2 - 35-39
3 - 40-44
4 - 45-49
5 - 50-54
6 - 55-59
7 - 60-64
8 - 65-69
9 - 70 and over

Age at Onset (First definitive diagnosis of a neoplasm)

Follow the code of Column 10, except for Y which can be disregarded.

Survival Period (From onset to date of report or death)

0 - Unknown or not given
1 - 0-5 months
2 - 6-11 months
3 - 12-17 months
4 - 18-23 months
5 - 24-29 months
6 - 30-35 months
7 - 36-47 months
8 - 48-59 months
9 - 60 and over months

Type of Tumor - Histogenic Classification
(American Cancer Society Code)

Column 13 - Tens
Column 14 - Digits

Tumors of Glandular Epithelium (00-09)

00 - Ductal tumor
01 - Tumor of mucinous secreting epithelium
02 - Papillary tumor, not elsewhere classified
03 - Neoplastic cyst, not elsewhere classified
04,05 - Functionally active tumors
06,08 - Other specific glandular tumors
09 - Unspecified tumors of glandular epithelial origin

Tumors of Nonglandular Epithelium (11-14)

11 - Tumor of transitional epithelium
12 - Tumor of basal epithelium
13 - Tumor of baso-squamous epithelium
14 - Tumor of squamous epithelium
15,16 - .....

Tumors of Melanin Forming Tissue (17)

17 - Tumor of melanoblast

Tumors of Epithelium, not elsewhere classified (18-19)

18 - Specific tumors of epithelium, not elsewhere classified
19 - Unspecified tumors of epithelial origin

Leukemias (20-29)

20 - Lymphocytic leukemia
21 - Monocytic leukemia
22 - Granulocytic leukemia
23,25 - .....
26 - Compound leukemias
27 - Leukemia and lymphoma
28 - Other specific leukemias
29 - Leukemia, type not specified

Lymphomas (30-39)

30 - Lymphosarcoma
31 - Reticulum cell sarcoma
32 - Hodgkin's disease
33 - Plasma cell myeloma
34 - Giant follicular lymphoma
35 - .....

Column

13-14 (Cont.) Type of Tumor - Histogenic Classification

Lymphomas (Cont.)

36 - Compound lymphomas
37 - .....
38 - Other specific lymphomas
39 - Lymphoma, type not specified

Tumors of Nervous Tissues and Associated Structures (40-49)

40 - Tumor of ganglion
41 - Tumor of sympathicoblast
42 - Tumor of neuroepithelium
43 - Tumor of paraganglion
44 - Argentaffinoma
45 - Tumor of peripheral nerve sheath
46 - Tumor of meninges
47 - Tumor of glia
48 - Other specific tumors of nervous tissue and structures
49 - Unspecified tumors of nervous tissue origin

Tumors of Vascular Tissue (50-59)

50 - Tumor of blood vessel
51 - Hemangiomatosis
52 - Multiple hemorrhagic hemangioma of kaposi
53 - Tumors of specialized vascular structures
54 - Tumor of lymph vessel
55,57 - .....
58 - Other specific tumors of vascular tissue
59 - Unspecified tumors of vascular tissue origin

Tumors of Muscle (66-69)

66 - Tumor of smooth muscle
67 - Tumor of striated muscle
68 - Other specific tumors of muscle
69 - Unspecified tumors of muscle origin

Tumors of Connective Tissue (70-77)

70 - Tumor of fibrous tissue
71 - Tumor of mucinous connective tissue
72 - Tumor of lipoid tissue
73 - Tumor of cartilage
74 - Giant cell tumor
75 - Ewings sarcoma
76 - Tumors of osseous tissue, not elsewhere classified
77 - Tumors of serous and synovial surfaces

13-14 (Cont.) Type of Tumor - Histogenic Classification

Tumors of Nonepithelial Tissues, not elsewhere classified (78-79)

78 - Specific tumors of nonepithelial tissue, not elsewhere classified
79 - Unspecified tumors of nonepithelial tissue origin

Tumors of Embryonal and Mixed Tissues (80-89)

80 - Tumor of trophoblast
81 - Tumor of embryonal gonadal tissue
82 - Tumor of teratoid tissue
83 - Tumor of epithelial and mesodermal tissues
84 - Tumor of epithelial and lymphoid tissues
85 - Tumor of mixed tissues, salivary gland type
86 - Tumor of dental tissues
87 - Tumor of mesenchyme
88 - Other specific tumors of embryonal and mixed tissues
89 - Unspecified tumors of embryonal and mixed tissue origin

Tumors, not elsewhere classified (97-99)

97 - Tumors of uncertain histologic type-no agreement as to classification
98 - Tumors of specific tissues, not elsewhere classified
99 - Tumor, cancer, neoplasm, and other general and nonspecific terms

Other Conditions (XX, X8 and X9)

XX - No information
X8 - Not a neoplasm
X9 - Diagnosis not completed, possibly a neoplasm

15 Type of Tumor - Degree of Malignancy

General Malignancy Code (Used with all Histogenic Code Numbers except Code Numbers 20-39)

X - Not a neoplasm, no premalignant significance
0 - Not a neoplasm, but having premalignant significance
1 - Benign neoplasm, no premalignant significance
2 - Benign neoplasm, but having premalignant significance

5 (Cont.)

Type of Tumor - Degree of Malignancy

General Malignancy Code (Cont.)

3 - Diagnosis not completed, suspected malignancy
4 - Neoplasm, malignancy not determined
5 - Malignant neoplasm, non-infiltrating (including carcinoma in situ)
6 - Malignant neoplasm, differentiated
7 - Malignant neoplasm, undifferentiated (anaplastic)
8 - Malignant neoplasm, differentiation not determined
9 - Malignant neoplasm, metastatic site

Leukemia Malignancy Code (Used with Histogenic Code Numbers 20-29)

5 - Aleukemic, not otherwise specified
6 - Chronic
7 - Acute
8 - Not determined

Lymphoma Malignancy Code (Used with Histogenic Code Numbers 30-39)

1 - Specified as benign (except the term "benign lymphoma")
6 - Single
7 - Multiple
8 - Multiplicity not stated

16-17 (Note double punching for melanomas 60-65)

Primary Site (Based on Maryland State Cancer Program Code)

Column 16 - Tens
Column 17 - Digits

Buccal Cavity and Pharynx	International Classification Number
00 - Lip, upper	140A
01 - Lip, lower	140B
02 - Lip, unspecified	140C
03 - Tongue	141
04 - Floor of mouth	143
05 - Salivary Gland	142
06 - Other and unspecified parts of mouth	144
07 - Oral nasopharynx	145
08 - Nasopharynx	146
09 - Hypopharynx	147
0X - Pharynx, other and unspecified parts	148

Column 16-17 (Cont.)

Primary Site	International Classification Number
Digestive System and Peritoneum	
10 - Esophagus	150
11 - Stomach	151
12 - Duodenum	152A
13 - Small intestine	152B
14 - Large intestine, except rectum	153
15 - Rectum	154
16 - Biliary passages	155A
17 - Liver	155B
18 - Pancreas	157
19 - Peritoneum	158
1X - Unspecified digestive organs	159
Respiratory System	
20 - Nose, nasal cavities, and middle ear	160A
21 - Accessory sinuses	160B
22 - Larynx	161
23 - Trachea	162A
24 - Bronchus and lung	162B
25 - Media stinum	164
2X - Other and unspecified thoracic organs	165
30 - Breast	170
Genital Organs	
40 - Cervix uteri	171
41 - Corpus uteri	172
42 - Other specified parts of uterus	173
43 - Uterus, unspecified parts	174
44 - Ovary and oviduct	175A,175B
45 - External and unspecified female genital organs	176
47 - Prostate	177
48 - Testis	178
49 - Penis	179A
4X - Other and unspecified male genital organs (scrotum)	179B
Urinary System	
50 - Kidney	180
51 - Bladder	181A
55 - Other and unspecified parts of urinary system	181B

Column

16-17 (Cont.)

Melanoma
Double Punch
Digit column Y
Eg Y
60

Primary Site	Melanoma	Other Types
Skin		
Other Types		
60 - Skin of lip	190A	191A
61 - Skin of face, head, neck	190B	191B
62 - Skin of upper extremities	190C	191C
63 - Skin of trunk	190D	191D
64 - Skin of lower extremities	190E	191E
65 - Skin, unqualified	190F	191F
Soft Tissue		
66 - Soft tissues of face, head, neck		197A
67 - Soft tissues of upper extremities		197B
68 - Soft tissues of trunk		197C
69 - Soft tissues of lower extremities		197D
6X - Other and unspecified soft tissues		197E

(Note: This group will include neoplasm of peripheral nerves which are coded to 193 of the International List.)

Bones		
70 - Jaw bone		196A
71 - Bones of head and face		196B
72 - Bones of upper extremities		196C
73 - Bones of trunk		196D
74 - Bones of lower extremities		196E
75 - Bones, unspecified sites		196F
Brain and Other Parts of Central Nervous System		
76 - Eye		192
77 - Brain		193A
78 - Other central nervous system and intracranial nerves		193B
Lymphatic and Hematopoietic System		
80 - Reticulum cell sarcoma		200.0
81 - Lymphosarcoma		200.1
82 - Other malignant neoplasm of lymphoid tissue		200.2

Column

16-17 (Cont.)

Primary Site	International Classification Number
Lymphatic and Hematopoietic System	
83 - Hodgkin's disease	201
84 - Giant follicular lymphoma	202.0
85 - Other forms of lymphoma	202.1
86 - Multiple myeloma	203
87 - Lymphatic leukemia	204.0
88 - Myeloid leukemia	204.1
89 - Monocytic leukemia	204.2
8X - Other and unspecified leukemia	204.3,204.4
8Y - Mycosis fungoides	205
Malignant Neoplasm of Other Sites	
90 - Thyroid	194
91 - Adrenal	195A
92 - Pituitary	195B
93 - Thymus	195C
94 - Pineal	195D
95 - Other and unspecified endocrine glands	195E
96 - Other specified sites	199A
9X - Unspecified sites or unknown	199B

18 **Stage of Disease**

0 - Unknown, not given, or pre-cancerous
1 - Early local, confined to primary site with no evidence of metastases and no extension
2 - Advanced local, no evidence of distant metastases but extension to adjacent anatomical sites
3 - Regional nodes and/or extension to adjacent anatomical sites
4 - Distant metastases, including extensive spread to adjacent anatomical sites
5 - Recurrence, original site
6 - Recurrence, metastatic site

19 **Metastatic Sites**

X - Regional nodes
Y - Local extension
0 - Unknown, not given, or none
1 - Remote metastases, bones upper extremities
2 - Remote metastases, bones lower extremities
3 - Remote metastases, bones spine
4 - Remote metastases, bones skull

19 (Cont.) Metastatic Sites

5 - Remote metastases, mediastinum
6 - Remote metastases, lungs
7 - Remote metastases, liver
8 - Remote metastases, brain
9 - Remote metastases, generalized

20 Original Diagnosis

0 - Unknown or not given
1 - Medical department of the company
2 - Private physician
3 - Public clinic
4 - Self or other

21 Method of Diagnosis

0 - Unknown or not given
1 - Periodic examination
2 - Special study
3 - Symptoms
4 - Other

22 Treatment

X - Hormone
Y - Chemotherapy
0 - No treatment or unknown
1 - Surgery
2 - Surgery with X-Ray
3 - Surgery with radium
4 - Surgery with radioactive isotope
5 - X-Ray only (Radiation)
6 - Radium only
7 - Radioactive isotope only
8 - X-Ray and radium or isotope

23-24 Present or Last Occupation in Petroleum Industry

Column 23 - tens
Column 24 - digits

00 - Unknown, not given, or none

Production

01 - Rigger and driller
02 - Well puller
03 -
04 -
05 - Others with frequent exposure to crude petroleum
06 -
07 -
08 -
09 - Others with infrequent exposure to crude petroleum

Column

23-24 (Cont.) Present or Last Occupation in Petroleum Industry

Refining

20 - Catalytic cracking (includes thermal cracking of catalytic feeds) - Operators
21 - Catalytic cracking (includes thermal cracking of catalytic feeds) - Laborers, still cleaners, etc.
22 - Thermal cracking - Operators
23 - Thermal cracking - Laborers, still cleaners, etc.
24 - Coking operations - Operators
25 - Coking operations - Laborers, still cleaners, etc.
26 - Blending of heavy fuel oils (#3-6)
27 - Blending of heating oil (#2)
28 -
29 - Others on cracking operations
30 - Refining and blending of lubricants - Operators
31 - Refining and blending of lubricants - Laborers, still cleaners, etc.
32 - Packaging of lubricants
33 - Manufacture and packaging of greases
34 -
35 - Others - lubricants and greases
36 - Refining and filtration (pressing or centrifugation) of paraffin - Operators
37 - Refining and filtration (pressing or centrifugation) of paraffin - Laborers, still cleaners, etc.
38 - Packaging of paraffin
39 - Others - paraffin
40 - Distillation of crude oil - Operators
41 - Distillation of crude oil - Laborers, still cleaners, etc.
42 - Production of asphalt - Operators
43 - Production of asphalt - Laborers, still cleaners, etc.
44 -
45 -
46 -
47 -
48 -
49 - Straight run distillations - Others
50 - White oil manufacturing - Operators
51 - White oil manufacturing - Laborers, still cleaners, etc.
52 -
53 -
54 -
55 -
56 - Petro-chemical operations - Operators
57 - Petro-chemical operations - Laborers, still cleaners, etc.

Column

23-24 (Cont.) Present or Last Occupation in Petroleum Industry

Refining (Cont.)

58 -
59 - Special products - Others
60 - Maintenance - Pipe Fitters
61 -
62 - Maintenance - Boilermakers
63 - Maintenance - Mechanics
64 - Maintenance - Tank Cleaners
65 -
66 -
67 -
68 -
69 - Maintenance - Others
70 -
71 - Loading department
72 -
73 -
74 -
75 -
76 - Control laboratory
77 -
78 -
79 - Others not otherwise specified - General Refining Operations

Transportation

80 -
81 -
82 -
83 -
84 -
85 - Pipe line workers
86 - Marine division - Transportation of light and medium distillates (end boiling point $\leq 650^{\circ}$)
87 - Marine division - Fuel oil carriers
88 - Fuel oil carriers - Others
89 - Transportation - Others

Marketing and Executive

90 - Service stations
91 -
92 -
93 -
94 - Others - Distribution
95 - Others - Office workers, etc.
96 -
97 -
98 -

Column

23-24 (Cont.) Present or Last Occupation in Petroleum Industry

Others (Not included in the four main divisions)

99 - Job to be described in detail on card

25 Approximate Number of Years Employed in the Petroleum Industry Prior to Onset

0 - Unknown, not given, or none
1 - 0-1 year
2 - 2-4 years
3 - 5-9 years
4 - 10-14 years
5 - 15-19 years
6 - 20 and over years

26-27 Principal Occupational Assignments in the Petroleum Industry (2/3-3/4)

Follow the code of Column 23-24

28 Approximate Number of Years so Engaged in Principal Assignments

Follow the code of Column 25

29-30 Secondary Occupational Assignments in the Petroleum Industry

Follow the code of Column 23-24

31 Approximate Number of Years so Engaged in Secondary Assignments

Follow the code of Column 25

32 Principal Petroleum Product Contact

The information will be punched as a secondary petroleum contact if only one product is listed and if the exposure is described as rare, infrequent, or light.

0 - No contact
1 - Not given or unspecified petroleum products
2 - Crude petroleum, reduced crude, asphalts
3 - Gasoline, light ends, and solvent naphthas ($< 400^{\circ}$ F.)
4 - Medium distillates ($400\text{-}650^{\circ}$ F.)
5 - Lube distillates and related uncracked intermediates ($600\text{-}1000^{\circ}$ F.)
6 - Refined products
7 - Products derived from thermal cracking units in refineries before or without catalytic cracking ($600\text{-}1000^{\circ}$ F.)

Column

32 (Cont.) Principal Petroleum Product Contact

8 - Products derived from coking operations (> 600° F.)
9 - Products derived from catalytic cracking and reforming processes or from thermal cracking units in refineries with catalytic crackers (600-1000° F.)
X - Chemical additives
Y - Petro-chemicals

33 Approximate Number of Years so Exposed

X - No exposure
0 - Unknown or not given
1 - 0-1
2 - 2-4
3 - 5-9
4 - 10-14
5 - 15-19
6 - 20 and over

34 Secondary Petroleum Contact

Follow the code of Column 32

0 - No exposure in any degree

35 Approximate Number of Years so Exposed

Follow the code of Column 33

X - No exposure

36-37 Principal Other Occupation - Punch as Coded

Column 36 - Tens
Column 37 - Digits

00 - Unknown. not given, or none

Professional and Semi-Professional

01 - Doctors, lawyers, clergymen, dentists, pharmacists, chemists, chiropractors, veterinarians, optometrists
02 - Midwives
03 - Nurses
04 - Students
05 - Teachers
06 - Auditors, clerical workers, bookkeepers, secretaries, draftsmen, tellers, stenographers, telephone and telegraph operators, cashiers, librarians, accountants, paymasters

Column

37 (Cont.) Principal Other Occupation

Professional and Semi-Professional (Cont.)

07 - Technicians, photographers, musicians, artists, assayers
08 - Other professional and semi-professional theatrical people, reporters, publishers, undertakers, opticians, managers of theaters, civil and mechanical engineers, dieticians
09 - Housewives

Proprietors

(10-19 inclusive apply only to people who own their own business)

10 - Store owners (sellers of merchandise, not food). jewelers, furriers, clothing stores, hardwood, art stores, florists, etc.
11 - Store owners (of food). grocers, stalls in market, produce dealers. bakers, oyster business, ice business, huckster
12 - Cafe and restaurant owners, saloon keepers
13 - Barbers, cleaners, laundry hairdressers
14 - Turners. plumbers, paper hangers, contractors, cabinet makers, shoemakers, tailors, stone cutters, blacksmiths, sheet metal, printers, upholsterers, carpenters
15 - Painters
16 - Garages
17 - Manufacturers (small) (not food) (food under 11)
18 - Junk dealers
19 - Other business (owner), funeral directors, owner of business (business unknown), organ builder, taxi proprietor, farmer, hauling, pool room, coal and wood, real estate

Skilled Labor

20 - Craftsmen (men with specific trades demanding a certain amount of specialized skill). Wheelwright, millwright, glaziers, coppersmiths, glass blowers, tool makers, carpenters, plumbers, electricians, machinists, cabinet makers, pattern makers, surveyors, silver engravers, paper hangers, tinners, printers, wood-workers, mechanics, lineman, slaters
21 - Blacksmiths, pipe fitters, boiler makers, brass molders, riveters, welders, sheet metal workers
22 - Stone masons, cement workers, bricklayers, plasterers, pottery makers, brickmakers

Column

.37 (Cont.) Principal Other Occupation

Skilled Labor (Cont.)

23 - Marine and stationary engineers and firemen, railroad engineers and firemen
24 - Railway men (steam and street), dispatchers, motormen, conductors, signalmen. brakemen
25 - Painters
26 - Taxi drivers, truck drivers, chauffeurs
27 - Mechanics (garage)
28 - Tailors, dressmakers, shoemakers, milliners
29 - Others. Jockeys, ship fitters, crane operators, lumber inspectors, simplex operators, watchmakers, tiremakers, riggers, jewelers, car repairmen, tractor drivers, tar men (Trade apprentices are in their specific trades.)

Sales and Service

30 - Interior decorators, window dressers, salesmen and clerks in stores (not food handlers)
31 - Workers in food trades, salesmen, hucksters, milkmen, brewers, millers in food stores, ice handlers, bakers, sugar testers, meat dealers, canning, pickling, oyster shuckers
32 - Workers in slaughter houses, meat packers
33 - Waiters, waitresses, stewards, bartenders, butlers, chefs
34 - Barbers, hair dressers, manicurists, matrons, masseurs
35 - Cleaners, laundry workers
36 - Commercial travelers, insurance agents, insurance collectors, tax collectors, real estate agents, insurance adjusters, credit investigators
37 - Policemen, firemen, mail carriers, city inspectors and guards
38 -
39 - Other miscellaneous sales and services, U. S. Army and Navy, Marine pilot, gas station attendants, manager of paper routes, weather bureau observer, manager hotel store room, foreman coal company, meter readers, carpet and linoleum layers, sea captains, salesmen (business unknown), paker (business unknown), bill-poster

Factory Workers and General Laborers

40 - Factory workers, clothing, shoes
41 - Factory workers (others), machine operators, upholsterers, still men, furniture finishers, awning makers, bookbinders, cigar makers, nickel platers, brass polishers, brush makers, coopers, grain handlers

Column

36-37 (Cont.) Principal Other Occupation

Factory Workers and General Laborers (Cont.)

42 - Janitors, watchmen, orderlies, porters, sextons, parlor car porters, elevator tenders, window washers, dish washers
43 - Domestics, cooks, housemaids. maids, laundresses, charwomen, housework by day, nursemaids
44 - Day laborers, street cleaners, stevedores, garbage collectors, farm hands, hostlers, (wood workers, if colored)
45 -
46 -
47 -
48 -
49 - Factory worker (factory unknown)

Miscellaneous

50 - Newsboy, messenger boys, errand boys, ushers, bootblacks, movie operators, bundle wrappers
51 -
52 -
53 -
54 -
55 -
56 -
57 - Ragmen, light housekeepers, miscellaneous odd jobs, car parkers, lamp lighters, pin setters, pugilists, gardeners, attendants at public baths, grave diggers
58 - Invalids
59 - Mentally deficient
5X - Reform school

38 Approximate Number of Years Employed at Principal Other Occupation - Punch as coded

0 - Unknown or not given
1 - 0-1 year
2 - 2-4 years
3 - 5-9 years
4 - 10-14 years
5 - 15-19 years
6 - 20 and over years

39 Exposure to Irritants Other Than Petroleum - Principal ~~Principal~~ Physical Agents

Separate Col.

1 - Trauma
2 - Radiant Heat
3 - Solar or Ultraviolet Rays
4 - Radioactive Substances or Roentgen Rays

Column

39 (Cont.) Exposure to Irritants Other Than Petroleum (Cont.)

Inorganic Substances

5 - Arsenic
6 - Chromates

Organic Substances

7 - Aromatic Amines
8 - Tar, Pitch, Creosote and Anthracene Oils
9 - Soot
X - Others (Specified in detail)
0 - Unknown, not given, or none

40 Approximate Number of Years Exposed to Principal Irritants Other Than Petroleum

0 - Unknown, not given, or none
1 - 0-1 year
2 - 2-4 years
3 - 5-9 years
4 - 10-14 years
5 - 15-19 years
6 - 20 and over years

Degree of Exposure to Principal Irritant Other Than Petroleum

0 - Unknown, not given, or none
1 - Heavy and continuous
2 - Heavy and occassional
3 - Heavy, amount not indicated
4 - Light but continuous
5 - Light but occassional
6 - Light, amount not indicated

Secondary Irritant Other Than Petroleum Products

Follow the code of Column 39

Approximate Number of Years Exposed to Secondary Irritant Other Than Petroleum Products

Follow the code of Column 40

Degree of Exposure to Secondary Irritant Other Than Petroleum Products

Follow the code of Column 41

SOCONY MOBIL OIL COMPANY, INC.

26 Broadway, New York 4, N. Y.

31 August 1955

Mr. David V. Stroop
American Petroleum Institute
50 W. 50th St.
New York, N. Y.

Dear Dave:

Allan Dooley of the Texas Company alerted us to the two attached articles on Cutting Oil Cancer which appeared in the British Journal of Industrial Medicine, 1955, 12, 240 and 244.

Dr. Saunders has reviewed these papers and we both think it would be an excellent idea to distribute copies of them to the Medical Advisory Committee and also to members of the new API Interdivisional Committee on Labels.

Very truly yours,

A. C. Pabst

A. C. Pabst
Industrial Hygienist
Medical Department

ACP:jd
attach.

Copy From D. V. Stroop For Information of Members of Medical Advisory Committee 9/6/55

API 06101

Brit. J. industr. Med., 1955, 12, 244.

CUTTING OILS AND SQUAMOUS-CELL CARCINOMA

PART II: AN EXPERIMENTAL STUDY OF THE CARCINOGENICITY OF TWO TYPES OF CUTTING OILS*

BY

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(RECEIVED FOR PUBLICATION JANUARY 25, 1955)

That mineral oils and their derivatives would induce squamous-cell carcinoma when painted on to the skin of mice was reported by Twort and Twort (1931), and in a series of other papers by these authors which have since been statistically analysed by Irwin and Goodman (1946). More recent work has demonstrated that both straight-run distillates (Woodhouse and Irwin, 1950) and high boiling point fractions of catalytically cracked petroleum oils (Smith, Sunderland, and Sugiura, 1951) may contain numerous carcinogenic hydrocarbons, although to date no pure carcinogens have been isolated from such compounds.

The literature which we have reviewed contains surprisingly few references to occupational cancers directly attributable to cutting oil exposure in the engineering industry. However, the relationship between excessive exposure to such products and a high incidence of other occupational skin diseases is well documented (Cruickshank, 1950; Shapiro, 1950).

Cruickshank and Squire (1950) have presented evidence, from both clinical observations and biological tests on mice and rabbits, implicating exposure to cutting oils as an occupational cancer hazard. A later publication by Cruickshank and Gourevitch (1952) supported this opinion. In the latter paper the authors suggested that it was quite possible that this cancer risk (exposure to cutting oils in the engineering industry) had not been long enough in existence for it to become apparent from mortality rate studies such as those of Henry (1947). It is interesting to note that in recent years the numbers and uses of the so-called "cutting fluids" have increased considerably. Such cutting fluids generally consist of a relatively stable aqueous emulsion of sulphurized petroleum oil distillates with vegetable and mineral oils in relatively small amounts and various cutting compound additives, including emulsifying, wetting, and penetrating agents. Disinfectants are also frequently added.

A preliminary report by Gilman and Vesselinovitch (1955) demonstrated that certain fractions of soluble cutting oil were capable of inducing a high incidence of tumours in the mouse. The fractions that proved carcinogenic were cut at 630, 800, and 930 F., under vacuum distillation to avoid cracking.

The present contribution is concerned with an analysis of the tumour responses obtained in several experiments involving prolonged exposure of mice to samples and dilutions of a soluble cutting oil as well as preliminary results obtained from tests using a straight cutting oil. Both of these products were cutting oils in use at the metal working plant referred to in Part I.

Cutting oils are generally sprayed in a continuous stream over the point of contact between the cutting edge of the machine tool and the metal being processed. At this point, minute quantities of the coolant are subjected to extremely high temperatures which might quite possibly cause cracking of the oils. The oil spray is collected under each machine and generally filtered through a system of weirs before returning to a sump for recirculation. Hence, one lot of oil, subject to periodic replenishment, frequently remains in use for several weeks.

Materials Tested

One of the cutting oils under investigation is marketed in the form of a water-soluble emulsion and is used in dilutions of one part to eight or more of water. As dilutions of this order might tend to obscure the presence of a weak carcinogen, tests were run using both the undiluted emulsion and various dilutions of this fluid. Samples of used cutting oils were also tested because it has been shown that cracking may greatly enhance the carcino-

* This work was supported in part by a grant-in-aid from the National Cancer Institute of Canada.

genicity of petroleum oils (Smith and others, 1951) and it seemed probable that the used oil might contain minute amounts of such cracked materials.

The properties of the two types of cutting oil and the several samples tested may be summarized as follows :

Cutting Oil A.—This is a soluble cutting fluid in the form of a stable oil-in-water emulsion containing active additives, about 45% sulphurized mineral oil base, and 40% water when marketed. It is usually diluted with eight or more parts of water before use.

Cutting Oil B.—This is a straight cutting oil, a sulphurized mineral oil blended with fatty oils. It is usually cut back with a low viscosity straight paraffin oil before use.

Samples Tested

Soluble Oil A-1-51	Undiluted ; unused (market product)
Soluble Oil A-1-53	As above—separate sample obtained over 12 months later
Soluble Oil A-2	Dilute 1 : 4 water ; unused
Soluble Oil A-3	Dilute 1 : 8 water ; unused
Soluble Oil A-4	Dilute approx. 1 : 8 water ; used*
Straight Oil B-1	Dilute 6 : 4 parts paraffin oil ; unused
Straight Oil B-2	Dilute 6 : 4 parts paraffin oil ; used.†

Methods

Samples of oil A were tested against C_3H, C_{57} black and R.F.‡ mice, while oil B was tested against C_3H mice only. Males and females were used in about equal numbers in all trials. Exposure consisted of painting the skin three times weekly with from 50 to 100 mg. of the test materials. The oils were applied with a camel-hair brush to a clipped area at the base of the neck.

Ages at the beginning of the experiments varied slightly but all groups fell within a range of from 90 to 130 days. Animals were housed in glass jars in groups of five and fed a standard commercial ration of fox cubes and rabbit pellets.

Calculations

Tumour response and carcinogenicity in this report are measured by means of the following simple statistics :—

(1) Mean Tumour Time (M.T.T.) $= \frac{\Sigma t}{TT}$

Where Σt = sum of the times in days to the appearance of the first tumour on each tumour-bearing mouse.

Where TT = total number of animals with either squamous-cell papilloma or carcinoma.

(2) Percentage tumours $= \frac{TT}{N_{corr.}} \times 100$

Where N = actual number of animals set up for each experiment.

Where $N_{corr.}$ = N less those mice that died without developing tumours before the M.T.T. minus two times its standard deviation.

(3) Percentage cancer $= \frac{C}{N_{corr}} \times 100$

Where C = total number of mice developing histologically confirmed squamous-cell carcinoma.

(4) Mean Non-tumour Survival Time (M.S.T.) $= \frac{\Sigma t_s}{N_{nt}}$

Where Σt_s = sum of survival times in days of all non-tumour mice, those still alive at the termination of the experiment being credited with survival times equal to the duration of the experiment in days.

Where N_{nt} = number of animals that failed to develop a tumour.

The M.S.T. is accompanied by a statement of the number of non-tumour survivors at the end of the experiment and its duration in days.

Results

Table I summarizes the results obtained from two separate tests of sample A-1 begun 18 months apart. In each of these trials a different batch of the soluble cutting oil A was used. Of the three strains of mice exposed, the C_3H and C_{57} black were inbred stock from our own colony while the R.F. mice, obtained commercially, were not necessarily inbred.

It will be readily noticed that there was, in both trials, an appreciable difference in response between the two inbred strains. This is expressed both in the percentage of tumours and to a less marked degree in the induction period (M.T.T.).

TABLE I

TUMOUR RESPONSE OF MICE TO SKIN PAINTING WITH A SOLUBLE CUTTING OIL AND WITH CORN OIL (CONTROL GROUP)

Sample	Strain	Number		Tumour Response: 310 Days' Exposure			Non-tumour Mice: End of Experiment		MST (days)
		N	N_{corr}	% Tumour	MTT (days)	% Cancer	Survivors	Days	
A-1-51	C_3H	20	18	61	204	22	2	401	232
	C_{57}Bl.	40	39	19	244	3	5	395	266
A-1-53	C_3H	38	36*	58	234	19	0	365	226
	C_{57}Bl.	30	30	27	255	3	1	406	256
	R.F.	30	30	33	144	7	0	310	109
Control	C_3H	20	—	0	—	0	9	401	340
	C_{57}Bl.	20	—	0	—	0	18	401	389

* Four deaths from injection occurred in a single cage between 161 and 175 days ; all animals showed similar necrotic liver and kidney lesions on necropsy. These four mice were discounted in calculating the response and MST.

Oil A proved highly toxic to the R.F. mice tested, with the result that this group had a non-tumour mean survival time (M.S.T.) of only 109 ± 35 days. Over 50% of the mice in this trial had died without

* Used for five weeks with daily replenishments with new emulsion
† Used for five weeks with daily replenishments with both new and unused oils.
‡ Rockland Farm mice—a commercial strain of albino mice obtained from Rockland Farms, New City, N.Y., U.S.A.

having developed a tumour before reaching the M.T.T. for the group as a whole (144 days). All the R.F. mice were dead by 310 days, and for this reason length of exposure has been chosen for the comparison between samples and strains shown in Table 1. The control groups of C_3H and C_{57} black were exposed to the same treatment as the test mice, except that they were painted with a domestic corn oil.

Regardless of the differences in response of the strains, it is quite evident that cutting oil A has, for a crude commercial product, quite a high tumour-inducing potency against mice and that this response shows a high level of repeatability.

In an initial investigation, the used oil (sample A-4) had shown only a very slight carcinogenic potency (Gilman, 1950–51, unpublished data). Consequently the tests summarized in Table 2 were undertaken, making use of similar dilutions of used (A-4) and unused (A-3) materials along with an unused intermediate dilution (A-2) of one part oil A to four parts of water. It was hoped that a comparison of the results obtained with these and with the undiluted product might help to clarify the role of dilution in reducing the tumour-producing activity of the used product.

TABLE 2

EFFECT OF DILUTION ON TUMOUR RESPONSE OF C_3H MICE TO SOLUBLE CUTTING OIL A

Sample	Dilution	Number		Tumour Response: 365 Days' Exposure			Non-tumour Mice: End of Experiment		MST (days)
		N	N corr.	% Tumour	MTT (days)	% Cancer	Survivors	Days	
A-1	None	30	26*	61·5	234	23·1	0	365	226
A-2	1 : 4	20	20	15·0†	291	0	3	456	323
A-3	1 : 8	20	20	0	—	0	0	456	335
A-4	1 : 8 (used)	20	20	0	—	0	15	412	396

* See footnote to Table 1.
† One of the papillomas in the 1 : 4 group regressed by 310 days.

The percentage of C_3H mice developing tumours from the 1 : 4 solution is slightly less than a quarter of that observed for the pure product, while the induction period (M.T.T.) had increased on the average about 70 days. Neither the used nor the unused 1 : 8 dilutions had elicited any response after exposure for a full year.

Mice of the apparently less susceptible C_{57} black strain were also exposed to the same dilution samples of the soluble oil as were used on the C_3H groups (Table 3). After 365 days' exposure the C_{57} group showed similar but on the whole somewhat less marked responses to the treatments.

TABLE 3

RESPONSE OF C_{57} BLACK MICE TO DILUTIONS OF SOLUBLE CUTTING OIL A

Sample	Dilution	Number		365 Days: % Tumour	Response at End of Exposure Period: % Tumour	MTT (days)	% Cancer	Duration (days)
		N	N corr.					
A-1	None	30	29	41	45	255	17	406
A-2	1 : 4	20	20	5	20	408	0	456
A-3	1 : 8	20	20	0	0	—	0	456
A-4	1 : 8 (used)	40	35	3	3	—	3	395

It is interesting to note that after 456 days the 1 : 4 group showed 20% tumours, a figure only slightly in excess of the response registered by the C_3H mice after 90 days less exposure time to the same treatment.

The results recorded in Table 4 for the straight cutting oil (samples B-1 and B-2) are from a pilot test involving too few animals and too short an exposure time to warrant the making of comparisons between these and the other cutting oil samples tested. However, sample B-1 was apparently responsible for skin tumours in two of the 10 animals exposed. One of these developed into a typical squamous-cell carcinoma and eventually metastasized to the lung.

TABLE 4

TUMOUR RESPONSE OF C_3H MICE TO STRAIGHT CUTTING OIL (BLENDED 6 : 4 WITH PARAFFIN OIL)

Sample	Number		% Tumour	MTT (days)	% Cancer	Days on Experiment
	N	N corr.				
B-1	10	10	20	162	10	328
B-2	16	16	0	—	0	295

Thus it would appear that this cutting oil is also carcinogenic, although confirmation of this and detail as to potency will have to await the completion of experiments in progress.

Discussion

The oil base of the soluble cutting oil tested is a 50–50 blend of sulphurized and filtered straight-run distillates of a crude mineral oil. These base oil fractions are supposedly not cracked and contain no additives other than commercial flowers of sulphur. Thus it might be expected that oil A would give a tumour response comparable to those reported for similar straight-run distillates. However, it would appear to be considerably more potent to the mouse than the several mineral oils and fractions tested by Woodhouse (1951, 1952) and his colleagues. This discrepancy in intensity of response suggests the possibility that one or more of the additives used in compounding the cutting fluid may be acting

synergistically with the mineral oils. None of these additives have been recorded in the literature reviewed as being either carcinogens or cocarcinogens; however, their possible role is being investigated at this laboratory.

The actual use of the cutting fluid A apparently does not either markedly reduce or enhance its tumour-producing potency. It had seemed possible that a reduction in carcinogenic activity might have been associated with oxidation of the carcinogenic components of the used oil, resulting possibly from extensive contact with metal particles. That oxidation may inhibit the potency of carcinogenic shale oil and synthetic tar has been shown by Twort and Twort (1930). However, in all probability the major part of those differences in response recorded in Table 2 is a simple function of the various levels of dilution. This contention is supported by evidence obtained from tests using $C_{3}/C_{3}H$ hybrids. Such hybrids are hardy, long-lived and resistant to the toxicity of the oils, yet seemingly susceptible to their carcinogenic properties. Twenty such mice, out of C_{3} mothers and therefore free from spontaneous mammary tumours, were treated with sample A-3 (1 : 8 dilution) in exactly the same manner as the other mice reported in Tables 2 and 3 except that exposure was prolonged through a period of 525 days. At 365 and 490 days these hybrids showed no response. However, by 525 days, with all 20 hybrids still living, three had developed tumours, one of which had become cancerous, a response approximating that of the $C_{3}H$ and C_{3} pure strain groups to the more concentrated 1 : 4 dilution after 365 and 456 days respectively. This suggests that, if exposure time to the various dilutions could be sufficiently extended, a tumour incidence comparable to that of the undiluted sample would ultimately be achieved. Apparently the induction period was the only variable appreciably affected by these dilutions. The advantage of using hybrid mice for testing substances that are highly toxic and where exposure may need to be continued over very long periods of time is also apparent.

These observations are of particular interest when it is remembered that it is with just such highly diluted oil-in-water emulsions that the machine operator is in contact. It is only to be expected that, if cutting oils are an aetiological factor in the occurrence of squamous-cell carcinoma amongst exposed workers, cases will probably be preceded by long periods of exposure. It would seem then that the length of the exposure period should be considered as a very important factor in the evaluation of results of experiments, such as those reported by Smith and others (1951), concerning the effect of dilution with an inactive material on the carcinogenicity of active fractions of catalytically cracked oils. These data seemingly influenced the interim recommendation by Holt, Hendricks, Eckardt, Stanton, and Page (1951) that blends of oil containing more than 10% of catalytically cracked oil boiling above 700° F. be considered carcinogenic.

Smith and Sunderland (1951) have reported differences in the response of various strains of mice to the same carcinogen. The evidence presented in this communication clearly supports their observations (Table 1). It appears advisable, therefore, to test against more than one strain of mice when attempting to determine whether or not a substance is carcinogenic. This would seem to be particularly important if the rabbit is not available for duplicate testing, in accordance with the suggestion of Hieger and Woodhouse (1952).

The inclusion of the mean survival time of those animals that failed to develop tumours along with the number of non-tumour survivors and the duration of each trial gives some indication of the reliability of the results in terms of the toxicity of the substances tested and response of the treated mice (other than tumour development) to the conditions of the particular experiment.

Summary

A soluble cutting fluid (oil-in-water emulsion) used in industry has been shown to be carcinogenic to three different strains of mice.

The response of test groups to a standard skin painting technique varied with the strain used from 19 to 61% tumours after 310 days' exposure.

Results proved reproducible and comparatively constant in two trials repeated after an interval of 18 months.

The responses in mice to 1 : 4 and 1 : 8 aqueous dilutions of this soluble oil were compared with the undiluted product and with a 1 : 8 used dilution after 365 days' exposure. A marked reduction in the percentage of mice bearing tumours and an increase in induction periods accompanied dilution.

Evidence was presented which suggests that the chief effect of dilution is the lengthening of the induction period. Thus when duration of treatment with a dilute oil was lengthened sufficiently the absolute tumour response approached that of mice exposed to the more concentrated emulsions.

Results of tests using a straight cutting oil (blend) are reported and suggest that this type may also be carcinogenic to the mouse.

The active interest in these investigations displayed by Dr. J. G. Cunningham (Director, Division of Industrial Hygiene, Ontario Department of Health), through whose division the original oil samples were obtained, is greatly appreciated by the authors.

We also wish to express our appreciation to Dr. J. D. Schroder of the Department of Pathology, Ontario Veterinary College, Guelph, who examined histopathologically all mouse tumour material discussed in this report.

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October 18, 1955

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

If the attached two articles have not been brought to the attention of the members of the Medical Advisory Committee of the API, it would probably be advantageous to see that they are circulated at least to the medical members of the committee.

Sincerely yours,

R. E. Eckardt

R. E. ECKARDT, M.D.

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Encs. - Cancer of the Respiratory Tract-
Recent Trends in Mortality, Edward
A. Law, J. of the International
College of Surgeons, Vol. 24, No.1,
July, 1955.

Accident Prevention in Childhood--
The Kerosene Hazard, H. A. Carithers,
J.A.M.A., Vol. 159, No. 2, Sept. 10, 1955.

Copy From D. V. Stroop For Information Of Members Of Medical Advisory Committee 10/28/55

API 06107

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Cancer of the Respiratory Tract

Recent Trends in Mortality

EDWARD A. LEW*

NEW YORK CITY, NEW YORK

THIS paper presents data on death rates from cancer of the respiratory tract in the general population of the United States and among Industrial and Ordinary policyholders of the Metropolitan Life Insurance Company.

Broadly speaking, these data indicate the following conclusions:

1. About half the increase in the number of deaths from respiratory cancer over the past twenty-five years reflects merely the growth of population and the greater proportion of persons at the older ages.

2. Respiratory cancer affects predominantly males past the age of 45 and females past the age of 55, the death rates among males being from four to six times those among females.

3. Respiratory cancer death rates past midlife are likely to continue rising.

4. In general, the magnitude of the respiratory cancer death rates reported from different parts of the United States appears to be associated with the quantity and quality of medical facilities available for accurate diagnosis of the disease.

5. Part of the increase in the reported incidence of respiratory cancer reflects improved diagnosis, more complete case finding, and more accurate reporting.

6. Part of the increase, however, undoubtedly represents a real rise in the incidence of respiratory cancer. While a number of factors have been suggested as being implicated in this increase, data are not available to show how much of the rise can reasonably be attributed to the effect of specific factors.

7. The highest respiratory cancer death rates in the white male population of the United States are found in the highly urbanized and industrialized states, and the lowest in the agricultural and mountain states.

8. Among white male Industrial policyholders, who are predominantly urban residents and employed for the most part in industry, respiratory cancer death rates have averaged from 30 to 50 per cent higher than among white males in the general population of the United States; however, the death rates among white female Industrial policyholders have been about the same as for white females in the general population.

9. Among male Ordinary policyholders, most of whom are drawn from the middle and better-to-do classes of the population engaged in nonhazardous occupations, respiratory cancer death rates have on the whole been somewhat lower than among white males in the general population.

The statistics in this paper relate to the broad category of respiratory cancer. In 1950, some 85 per cent of the deaths in this category were accounted for by cancer of the lung trachea and bronchus, as shown in Table 1:

*Actuary and Statistician, Metropolitan Life Insurance Company.

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TABLE 1.—*Deaths from Respiratory Cancer in the United States, 1950*

Detailed Site	Number of Deaths	Percentage of All Deaths from Respiratory Cancer
Trachea, Bronchus, and Lung Specified as Primary	7,618	35
Lung and Bronchus Unspecified as to Primary or Secondary	10,695	50
Larynx	1,852	9
Nose, Nasal Cavities, Middle Ear, Sinuses	645	3
Mediastinum	409	2
Thoracic Organs Secondary	284	1
Total	21,503	100%

Increase in Deaths From Respiratory Cancer.—During the past twenty-five years, mortality from respiratory cancer has risen so sharply in the United States that this once rare disease has now become an important cause of death, particularly among white males. In 1950, only diseases of the heart, vascular lesions of the central nervous system, cancer of the digestive system, hypertension and arteriosclerosis, and accidents (all forms) outranked respiratory cancer as a cause of death among white males at ages 55 and over.

The total number of deaths reported in the United States as due to respiratory cancer rose from 3,900 in 1930 to almost 27,000 in 1953, or about sixfold. If the toll from this disease continues to mount as it has in recent years, there will be about 40,000 such deaths reported in 1960.

As is brought out in Chart 1, approximately half the increase in the number of deaths from respiratory cancer reflects merely the growth of our population and a greater proportion of persons at the older ages, who are subject to higher death rates from this disease than younger persons. Hence, about half the increase in the number of such deaths represents a higher reported incidence of respiratory cancer. This is indicated in Table 2.

Among white males the number of deaths reported as due to respiratory cancer rose about sevenfold between 1930 and 1953. Among white females the corresponding increase was somewhat less than threefold. The relative increase in respiratory cancer deaths was even greater for nonwhite persons. However, the rather small number of such deaths reported among nonwhite persons in 1930 suggests that proportionately very many more cases of respiratory cancer were then being missed in the nonwhite than in the white population.

In each race and sex group with the exception of white females, somewhat less than half the increase in the number of respiratory cancer deaths reported between 1930 and 1953 was accounted for by the growth and aging of the population; among white females the corresponding proportion was about sixty per cent.

Increase in Deaths from Cancer of Other Sites.—Between 1930 and 1953 the

TABLE 2.—*Increase in Number of Deaths from Respiratory Cancer in the United States, 1930 to 1953*

	Number of Deaths 1953*	Number of Deaths 1930**	Total Increase	Increase in Deaths Due to: Higher Incidence	Increase in Deaths Due to: Growth and Aging of Population
Total persons	26,920	3,900	23,020	11,900	11,120
White males	20,930	2,650	18,280	9,800	8,480
White females	3,990	1,100	2,890	1,100	1,790
Nonwhite males	1,670	100	1,570	850	720
Nonwhite females	330	50	280	150	130

*Based on 10% sample of 1953 deaths in U. S. population.
**Adjusted to include Texas.

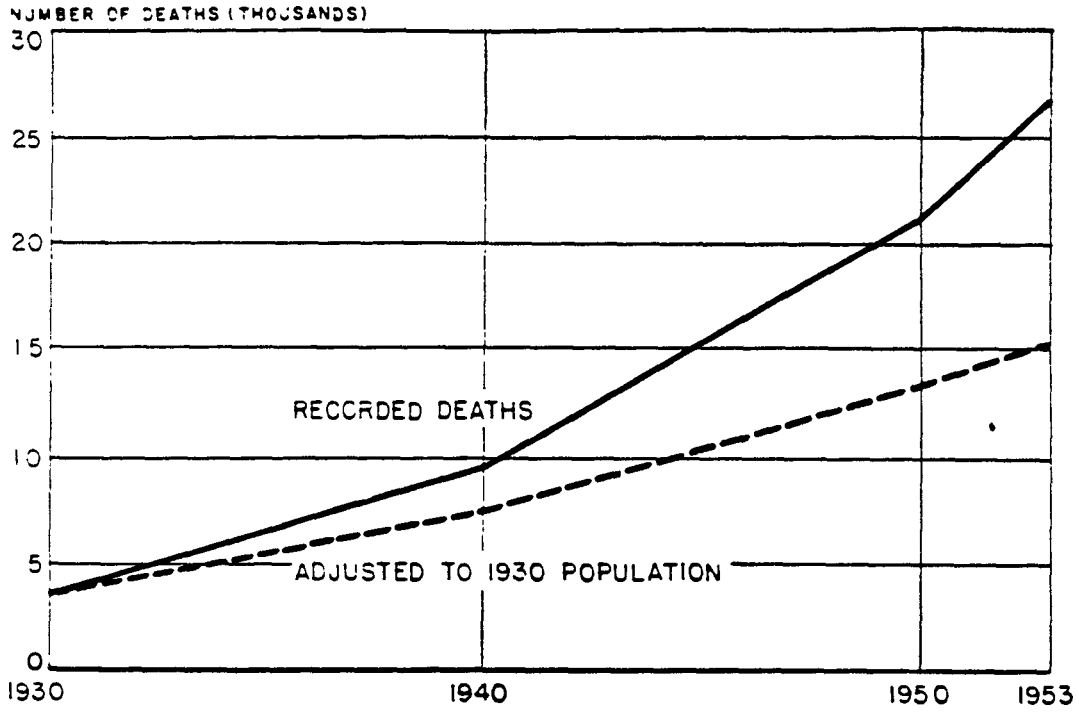

CHART 1.—Number of deaths from cancer of the respiratory tract in the United States in 1930, 1940, 1950 and 1953.

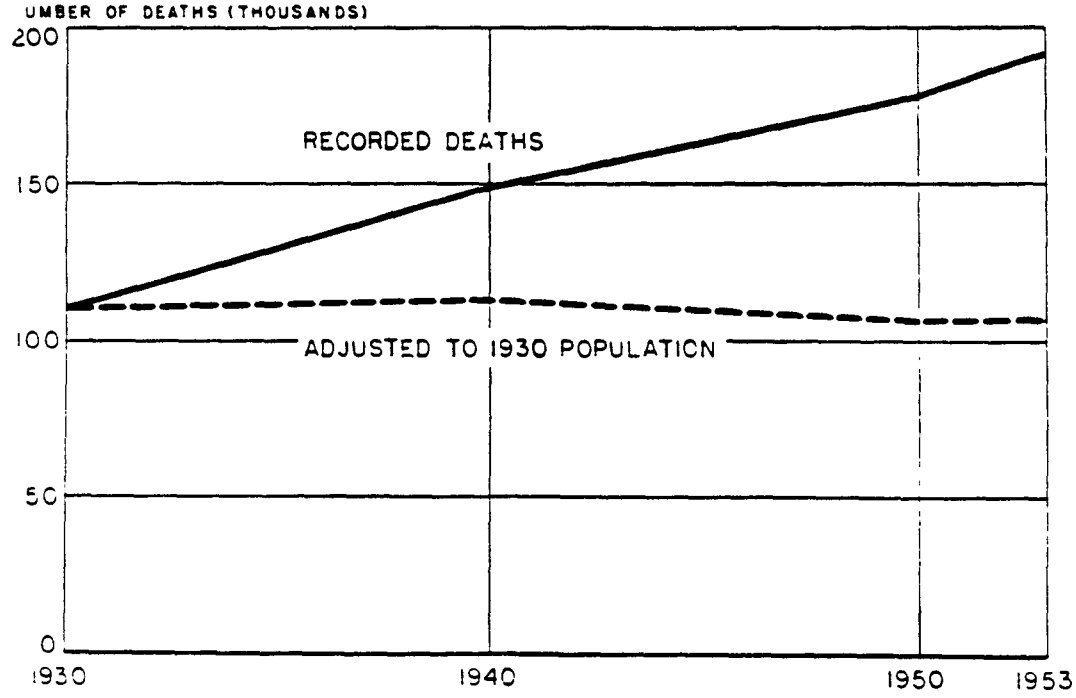

CHART 2.—Number of deaths from cancer of other sites in the United States in 1930, 1940, 1950 and 1953.

TABLE 3.—*Increase in Number of Deaths from Cancer Other Than Respiratory in the United States, 1930 to 1953*

	Number of Deaths 1953*	Number of Deaths 1930**	Total Increase	Increase in Deaths Due to: Higher Incidence	Increase in Deaths Due to: Growth and Aging of Population
Total persons	192,020	113,850	78,170	—3,730	81,900
White males	83,780	47,720	36,060	1,175	34,885
White females	92,280	59,100	33,180	—7,280	40,460
Nonwhite males	7,690	2,400	5,290	2,050	3,240
Nonwhite females	8,270	4,630	3,640	325	3,315

Based on 10% sample of 1953 deaths in U. S. population.
*Adjusted to include Texas

number of deaths reported in the United States as due to cancer other than of the respiratory system, rose from 114,000 to 192,000. (Here and elsewhere in this paper, the term "cancer" excludes the leukemias and Hodgkin's disease.) As is brought out in Chart 2, the entire increase in reported deaths from such cancers can be accounted for by the growth and aging of the population. This is indicated in Table 3.

The table also shows that when adjustment is made for the increase in deaths due to the growth and aging of the population, the number of deaths from cancer, other than of the respiratory system, has since 1930: (a) increased slightly for white males, (b) decreased about 12 per cent for white females, (c) nearly doubled for nonwhite males, and (d) increased about 7 per cent for nonwhite females.

The relatively much greater reported increase among nonwhite males than among white males, as well as the increase of such cancers among nonwhite females in contrast to a decrease in the age-adjusted incidence among white females, may be attributed to the substantial progress made in raising the standards of

TABLE 4.—*Respiratory Cancer Death Rates per 100,000 United States Population, 1930, 1940, and 1950*

Ages	White Males 1930	White Males 1940	White Males 1950	White Females 1930	White Females 1940	White Females 1950
25-34	.8	1.3	1.2	.6	.5	.5
35-44	3.4	6.0	7.9	1.7	1.7	2.2
45-54	10.7	23.8	39.1	3.7	6.3	6.5
55-64	20.1	47.4	95.9	9.5	12.8	15.5
65-74	26.4	53.8	119.4	11.7	18.4	27.2
75-84	21.8	51.7	109.1	9.7	18.3	40.0
85 & over	19.6	32.6	102.7	7.4	14.1	44.0

Ages	Nonwhite Males 1930	Nonwhite Males 1940	Nonwhite Males 1950	Nonwhite Females 1930	Nonwhite Females 1940	Nonwhite Females 1950
25-34	1.1	1.5	2.1	.1	.5	1.1
35-44	2.0	4.8	9.4	1.3	1.8	2.6
45-54	3.0	16.7	40.6	3.1	4.7	8.7
55-64	6.8	21.3	79.0	1.7	9.4	15.5
65-74	4.5	26.6	67.8	3.4	10.6	17.8
75-84	6.7	15.0	48.6	—	2.8	19.5
85 & over	—	6.3	10.7	6.7	—	19.1

diagnosis, case finding, and reporting of cancer in the nonwhite population closer to the level of those in the white population. Part of this may reflect the increasing exposure of the nonwhite population to modern medicine, as a result of large scale migration from the rural South to northern cities. The same developments have, of course, also been responsible for much of the increase in the reported incidence of respiratory cancer among nonwhites.

Respiratory Cancer Death Rates by Age, Sex and Race in the General Population.—The effect of population changes on the trend of respiratory cancer mortality can be eliminated by using death rates for specific age groups. Such death rates for each sex and race make it possible to investigate further the nature of the rise in respiratory cancer mortality. Table 4 and Charts 3 and 4 show such death rates for 1930, 1940, and 1950 in the general population of the United States.

The most striking feature of these trends is that the death rates have risen very much more rapidly for males than for females, even though as far back as 1930 respiratory cancer mortality was already much higher among males than among females. Between 1930 and 1950, the white male death rate from this disease increased by 130 per cent at ages 35-44, by 260 per cent in the age range 45-54, and from 350 per cent to 400 per cent at ages 55 and over. For white females, the increases were only 30 per cent at ages 35-44, about 70 per cent in the age range 45-64, 130 per cent at ages 65-74, and 340 per cent at ages 75 and over. As a result of these sex differences in trend, the overall death rate from respiratory cancer for white males had by

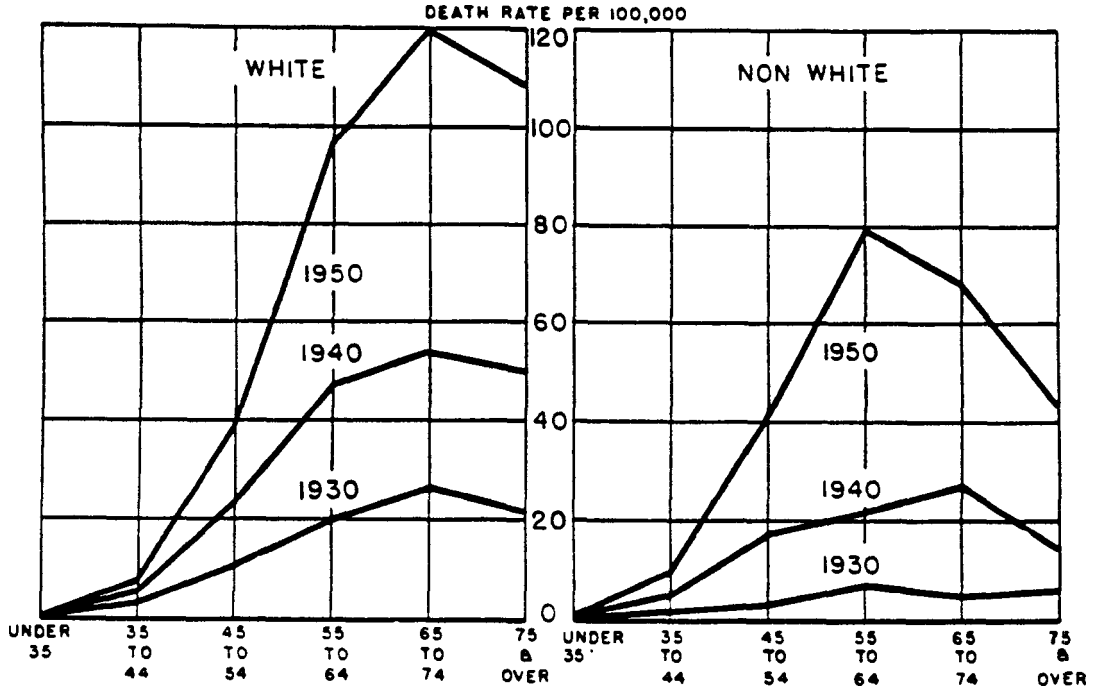

CHART 3.—Age pattern of male death rates from cancer of the respiratory tract in the United States in 1930, 1940 and 1950.

TABLE 5.—*Statistics on Cohort Basis*

White Male Cohort Born In	Respiratory Cancer Death Rates per 100,000 At Attained Ages				
	[illegible]	45-54	55-64	65-74	75-84
1855-1865				26.4	51.7
1865-1875			20.1	53.8	109.1
1875-1885		10.7	47.4	119.4	
1885-1895	3.4	23.8	95.9		
1895-1905	6.0	39.1			

1950 increased to about 4½ times that among white females, whereas in 1930 the corresponding difference had been only about 2¼ times. The disparity was greatest in the age range from 45 to 64, in which the 1950 death rates among white males were approximately six times those among white females; in the age range from 65 to 74 the male death rates were about four times the female rates.

In 1950, the deaths from respiratory cancer among white males at ages 55 to 64 accounted for 4.2 per cent of the total mortality in this age group: the corresponding figures at ages 45 to 54 and 65 to 74 were 4.0 per cent and 2.5 per cent, respectively. Among white females, the deaths from respiratory cancer accounted for only about 1.2 per cent of the total mortality in the broad age range 45-64.

Among nonwhite lives the ratio of male to female death rates from respiratory cancer has been about the same as among white lives. However, between 1930 and 1950 the respiratory cancer death rates increased more than tenfold for nonwhite males at ages 45 and over, and very appreciably, although not as rapidly, for nonwhite females.

The age-specific death rates from respiratory cancer have thus risen much faster in the nonwhite than in the white population. Consequently, by 1950 the nonwhite death rates from respiratory cancer had come to exceed the correspond-

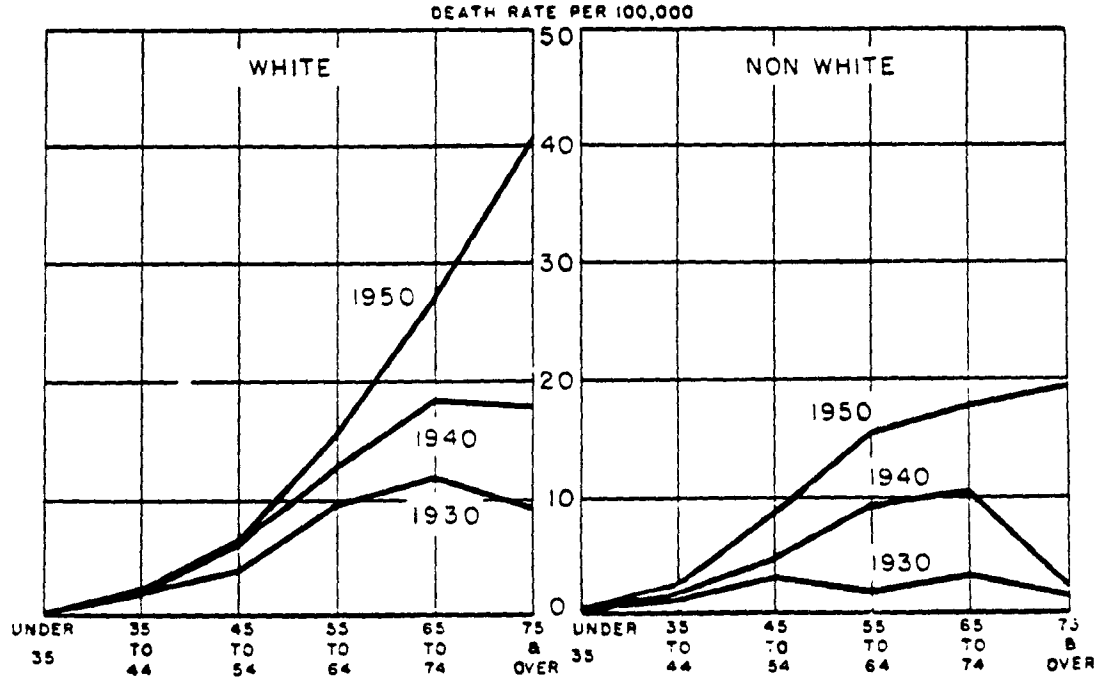

CHART 4.—Age pattern of female death rates from cancer of the respiratory tract in the United States in 1930, 1940 and 1950.

ing white death rates at ages under 55. While the reported death rates in 1950 for nonwhites at ages over 55 were still below the corresponding rates for whites, it is necessary to keep in mind that the reporting of deaths among older nonwhites is known to be somewhat deficient as to numbers and inaccurate both as to age and causes of death. If allowance could be made for the lower standards of diagnosis, case finding, and reporting of respiratory cancer in tnis segment of the nonwhite population, it is likely that the current death rates from this disease among nonwhites at these ages would turn out to be close to if not higher than the corresponding death rates among white lives.

It is quite clear that among both whites and nonwhites respiratory cancer takes its heaviest toll past midlife. For males under 45 and females under 55 death rates from this disease were all below 10 per 100,000 in 1950. At ages over 45 the death rates rise rapidly with advance in age. Among white males the death rates increase to a maximum at ages 65-74 (120 per 100,000 in 1950) and then decline somewhat. Among white females the death rates continue to rise to the oldest ages, the maximum being recorded at ages 85 and over (44 per 100,000 in 1950). Respiratory cancer death rates in England, Canada and other countries show the same characteristic earlier peak for males.

It has been suggested that one possible explanation of the earlier peak in the male death rates is that some new carcinogenic factor, to which a larger proportion of males than females are exposed, may have been operating on an increasing scale over the past three or four decades. If this factor also affected younger males to a greater degree than older males, then the cohorts of younger males who have been exposed to the increasing operation of this factor from an earlier age would be expected to show higher death rates than the cohorts of older men. The actual experience (in 1930, 1940, and 1950) of several cohorts of white males in the United States presented in Table 5, does show that the older cohorts have been subject to lower respiratory cancer death rates than the more recent cohorts.

If the hypothesis just mentioned is true, then the peak of the respiratory cancer death rates probably will shift to the more advanced ages, when the more recent cohorts attain the older ages.

The trend of the age-specific death rates from respiratory cancer indicates that the percentage increases in death rates from 1940 to 1950 were generally smaller than those from 1930 to 1940 for both whites and nonwhites in each sex; however, the absolute increases in death rates from 1940 to 1950 were greater than those from 1930 to 1940 in most of the age groups over 45. It appears, therefore, that the increase in respiratory cancer death rates is slowing down at the younger ages only. Judging by recent trends in the general population, further increases in

TABLE 6.—*Respiratory Cancer Death Rates per 100,000 Industrial Policyholders—Metropolitan Life Insurance Company 1930-32, 1940-42 and 1950-52*

	White Males			*White Females*		
Ages	*1930-32*	*1940-42*	*1950-52*	*1930-32*	*1940-42*	*1950-52*
25-34	1.1	1.2	1.3	.7	.4	.5
35-44	4.9	7.5	10.3	1.7	2.4	2.2
45-54	17.0	34.5	53.7	4.3	6.2	6.2
55-64	34.2	75.1	134.2	8.5	13.5	14.1
65-74	42.9	81.6	184.7	10.8	20.0	29.5

respiratory cancer death rates past midlife are to be expected.

Respiratory Cancer Death Rates by Age and Sex among Industrial Policyholders.— Industrial policyholders represent for the most part urban wage earners and their families. They are generally persons in the lower income brackets and include a high proportion of men engaged in manufacturing and mechanical industries, in mining, in transportation, and in personal service. The age-specific death rates from respiratory cancer among these insured lives thus shed light on the incidence of this disease in urban areas and among workmen in industry. Table 6 shows the age-specific death rates among white male and female Industrial policyholders of the Metropolitan Life Insurance Company in the periods 1930-1932, 1940-1942 and 1950-1952.

A notable feature of the death rates from respiratory cancer among Industrial policyholders is that they have been substantially higher than the rates in the general population for white males at ages 35 to 74, where as for white females they have been remarkably close to those in the general population at all ages. Over the years, the disparity in respiratory cancer death rates between white male Industrial policyholders and white males in the general population has been diminishing. In recent years, death rates from respiratory cancer among white male Industrial policyholders have exceeded those among white males in the general population by nearly a third in the age group from 35 to 44, by about two-fifths in the age range from 45 to 64, and by more than a half at ages 65 to 74. The death rates from cancer other than of the respiratory system have also been higher among white male Industrial policyholders than among white males in the general population, but the differentials have been much narrower, ranging from 5 per cent in the age group 35-44 to 20 per cent at ages 65-74. The death rates from nonrespiratory cancers among white female Industrial policyholders have been about the same as for white females in the general population.

The trend of the age-specific death rates from respiratory cancer among white Industrial policyholders indicates that for males at ages 45 and over the absolute increases in death rates from 1940-1942 to 1950-1952 were significantly greater than those from 1930-1932 to 1940-1942; for males at ages under 45, the absolute increases were about the same in both periods. For females the absolute increases from 1940-1942 to 1950-1952 were generally smaller than from 1930-1932 to 1940-1942. It seems, therefore, that the increase in respiratory cancer death rates is slowing down only among females or at best possibly also among males at the younger ages. Judging by recent trends among Industrial policyholders, respiratory cancer death rates may be expected to continue rising among males past midlife.

TABLE 7.—*Respiratory Cancer Death Rates per 100,000 Ordinary Policyholders—Metropolitan Life Insurance Company, 1930-32, 1939-40 and 1950-52*

Ages	White Males			White Females		
	1930-32	1939-42	1950-52	1930-32	1939-42	1950-52
25-34	1.5	0.9	1.1	0.7	0.8	0.6
35-44	4.2	5.2	7.2	2.1	2.9	2.3
45-54	11.8	22.2	34.5	5.3	7.7	5.8
55-64	25.6	49.2	87.5	9.0	17.5	19.8
65-74	31.4	62.4	145.1	9.6	35.9	39.8
75 & over	27.1	49.6	100.6	—	—	82.0

Respiratory Cancer Death Rates by Age and Sex among Ordinary Policyholders.—Ordinary policyholders are drawn chiefly from the middle and the well-to-do classes of the population engaged in non-hazardous occupations. The age-specific death rates from respiratory cancer among them, therefore, give some indication of the incidence of this disease among persons in the higher socio-economic groups of the population. Table 7 shows the age-specific death rates among male and female Ordinary policyholders of the Metropolitan Life Insurance Company during the periods 1930-1932, 1939-1940, and 1950-1952.

In the most recent period respiratory cancer death rates among males insured under Ordinary policies were on the whole lower than in the general population; by some 10 per cent lower in the age range from 35 to 64 and at ages 75 and over. However, in the age group from 65 to 74, respiratory cancer death rates among male Ordinary policyholders were about 20 per cent higher than in the general population. The generally lower death rates among Ordinary policyholders are in line with the recent findings on social class mortality in England and Wales,* which showed that in 1950 lung cancer mortality among men aged 20 to 64 in the two highest social classes (professional, managerial, etc., and intermediate occupations) was only about 80 per cent of that for all occupied and retired men.

The respiratory cancer death rates among female Ordinary policyholders at the ages of 55 and over have been somewhat higher than in the general population. This too is in line with the recent findings on social class mortality in England and Wales, which showed that in 1950 the lung cancer mortality of married women aged 20 to 64 in the three highest social classes was somewhat higher than the average for all married women.

The trend of the age-specific death rates from respiratory cancer among Ordinary policyholders indicates that for males aged 55 and over the absolute increases in death rates were significantly greater in the 1940's than in the 1930's; for males aged under 55 the absolute increases were about the same in both periods. For females aged 55 and over the absolute increases in death rates were very much smaller in the 1940's than in the 1930's; for females aged under 55 the death rates actually decreased during the more recent period. It appears, therefore, that the increase in respiratory cancer death rates is slowing down for females and perhaps also for males at the younger ages. Judging by recent trends among Ordinary policyholders, further increases in respiratory cancer death rates are to be expected for males past midlife.

Geographic Variations in Respiratory Cancer Death Rates.—Geographic variations in respiratory cancer death rates offer some clues as to the factors which may be implicated in the increased incidence of this disease. In considering such variations, it is necessary, however, to keep in mind that differences in death rates reported from various regions may be attributable to differences in the accuracy of diagnosis, case finding, and reporting as well as to the effect of specific factors.

Table 8 shows the age-specific death rates from respiratory cancer for white males in different regions of the United States in 1950. In general, the highest age-specific death rates were recorded in the Middle Atlantic and New England regions and the lowest in the East South Central, the West North Central, and the Mountain regions. The corresponding age-specific death rates from respiratory cancer for white females show no such clear

*The Registrar General's Decennial Supplement for England and Wales, 1951, Occupational Mortality, Part 1.

cut pattern and do not vary as much from one part of the country to another.

Table 9 and Chart 5 present age-adjusted death rates from respiratory cancer for white males in individual states. The highest death rates were recorded in Louisiana, New Jersey, District of Columbia, New York, Maryland, and Delaware (all in excess of 30 per 100,000). The lowest death rates prevailed in North Dakota, Arkansas, Idaho, New Mexico, North Carolina, and Utah (all below 15 per 100,000). Broadly speaking, the highly urbanized and industrialized states had high rates while the predominantly agricultural and mountain states had low rates. Contrary to this general observation, Louisiana had the highest age-adjusted death rate of all states (34.8 per 100,000), and high rates were also recorded in Florida (27.8 per 100,000) and Nevada (27.7 per 100,000). For white females, the highest death rates from respiratory cancer were also most often found in the highly urbanized and industrialized states (as well as in Louisiana, Florida, and Nevada). The 1940 respiratory cancer death rates by state presented much the same picture.

If in 1950 white males in the United States as a whole had shown the relatively high age-specific death rates from respiratory cancer observed in the Middle Atlantic States, the number of deaths from this disease among them would have been increased by about 25 per cent. If these

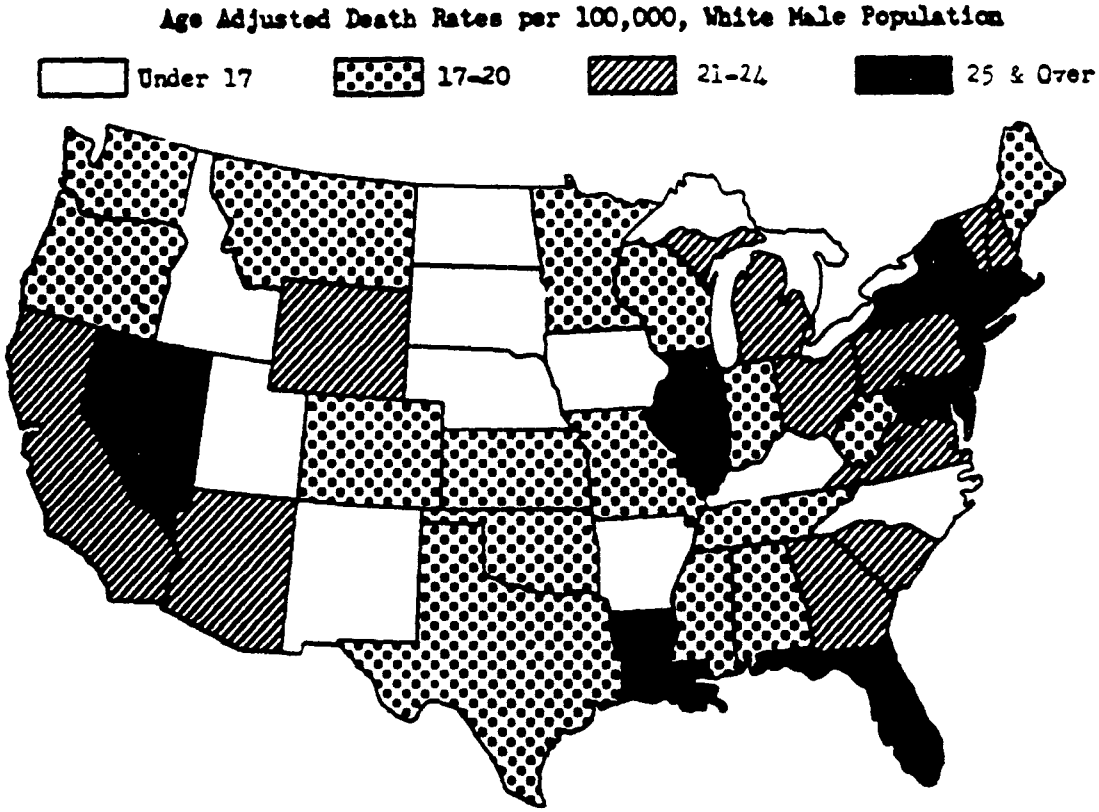

CHART 5.—Age distribution of cancer of the respiratory tract in the white male population of the United States in 1950.

TABLE 8.—*Geographic Variations in Respiratory Cancer Death Rates of White Males by Broad Regions of the United States—1950*

Region	Date Rate per 100,000					
	25-34	35-44	45-54	55-64	65-74	75 & over
New England	1.1	8.8	40.3	97.2	140.3	111.2
Middle Atlantic	1.3	8.8	47.8	121.4	165.6	139.9
East North Central	1.3	7.2	40.4	97.0	111.3	100.6
West North Central	1.1	6.5	26.8	69.5	85.2	90.2
South Atlantic	1.1	8.9	39.7	98.3	112.8	106.9
East South Central	1.1	9.1	32.3	65.9	70.7	81.1
West South Central	1.1	8.4	35.3	91.5	92.1	111.6
Mountain	1.6	4.2	29.7	61.8	109.7	92.2
Pacific	1.1	7.5	37.6	90.2	121.2	103.4
United States	1.2	7.9	39.1	95.9	119.4	108.3
Canada (1950-51)	0.7	4.5	27.5	72.7	101.4	82.6

men had experienced the age-specific death rates from respiratory cancer found in 1950 in England and Wales, the number of deaths among them from this disease would have been doubled.

For white males in the general population of Canada, the age-specific death rates from respiratory cancer were almost as low as those in the three regions of the United States mentioned above as having the lowest rates. In the Province of Ontario, the death rates were moderately higher, but still somewhat below the average for the United States as a whole. In the Metropolitan Life Insurance Company's experience among Industrial policyholders in Canada, white males also showed much lower death rates from respiratory cancer than white male policyholders in the United States, but white females showed about the same death rates in both countries.

Table 10 shows for each state the 1940 and 1950 crude (not age-adjusted) death rates from respiratory cancer for all persons combined, as well as the number (in 1940) of physicians per 100,000 population in the state. This latter ratio provides a rough measure of the medical facilities available for diagnosis and case finding. The comparison of the 1940 and 1950 crude death rates indicates that the incidence of respiratory cancer rose during the 1940's in every state. However, the smallest percentile increases occurred in the states with relatively high death rates in 1940 and the largest increases were reported from states that had low rates in 1940. This is consistent with the hypothesis that, in the past, geographic differences in respiratory cancer mortality reflected largely differences in the proportion of such cases detected and reported. With improvements in diagnosis and more complete case findings, the disparity between the states has diminished. It is not surprising to find that the states with relatively high numbers of physicians per 100,000 population reported high death rates from respiratory cancer. The magnitude of the reported death rates from respiratory cancer is clearly associated with the quantity and quality of the medical facilities available for accurate diagnosis of the disease.

Improved Diagnosis and More Complete Case Finding of Respiratory Cancer.—There is considerable evidence that developments leading to more careful and more frequent diagnostic study of patients as well as improvements in diagnostic techniques have played a very important part in the recorded rise of respiratory cancer death rates. This evidence cannot,

however, be translated into estimates of the proportions of deaths currently reported as due to respiratory cancer which twenty-five years ago would have been reported under cancer of other sites or as due to other diseases.

The more significant pieces of evidence are:

1. As a result of more and better instruction in diagnosis at both the undergraduate and graduate levels, there has been a great increase in the number of physicians with good training in diagnosis. The number of specialists in radiology and bronchoscopy has also increased markedly. Furthermore, the publicity given in the medical and lay press to the sharp rise in respiratory cancer has of itself led to greater awareness of this disease and thus to more frequent search for it.

2. The facilities available for diagnosis of respiratory cancer and their use have likewise multiplied. The growth and utilization of hospital facilities have been particularly marked since World War II. Impetus to the use of roentgen was given by the mass roentgen campaigns for tuberculosis detection even before World War II, and later by the large scale roentgen examinations for military service and in the armed forces. Industrial medical services have been expanded steadily and there, too, roentgen examinations have become almost routine. Of special importance has been the increase in accessibility of modern medical facilities to persons living in agricultural and outlying regions.

3. The development of better diagnostic methods (such as roentgen rays, bronchoscopy, cytologic examinations and diag-

TABLE 9.—*Geographic Variations in Respiratory Cancer Death Rates of White Males By States, 1950*

Age Adjusted Death Rate per 100,000

Region	Low (Under 17)		Medium Low (17-21)		Medium High (21-24)		High (25 and Over)	
New England			Me.	20.2	Vt.	21.6	Mass.	25.3
					N. H.	23.0	R. I.	27.0
							Conn.	29.3
Middle Atlantic					Pa.	24.5	N. Y.	33.5
							N. J.	34.2
East North Central			Wis.	17.8	Ohio	22.7	Ill.	26.1
			Ind.	20.7	Mich.	24.8		
West North Central	N. D.	11.8	Kans.	17.1				
	Neb.	15.2	Minn.	17.2				
	Iowa	16.0	Mo.	20.6				
	S. D.	16.4						
South Atlantic	N. C.	14.0	W. Va.	20.0	Ga.	23.0	Fla.	27.8
					Va.	23.5	Del.	30.9
					S. C.	23.8	Md.	32.0
							D. C.	34.0
East South Central	Ky.	15.2	Tenn.	17.3				
			Ala.	17.8				
			Miss.	20.2				
West South Central	Ark.	13.5	Okla.	19.9			La.	34.8
			Texas	20.9				
Mountain	Idaho	13.6	Colo.	18.2	Ariz.	23.6	Nev.	27.7
	N. Mex.	13.7	Mont.	20.1	Wyo.	23.8		
	Utah	14.9						
Pacific			Wash.	18.2	Calif.	24.8		
			Ore.	19.8				

TABLE 10.—*Death Rates from Respiratory Cancer and Physicians per 100,000 Population Increase in Death Rate from 1940 to 1950 Among All Persons By States*

State	Respiratory Cancer Death Rate per 100,000 1940	1950	% Increase	Physicians per 100,000*
South Carolina	1.9	8.5	347	74
Arkansas	2.2	8.3	277	94
Mississippi	2.4	8.1	238	69
North Carolina	2.7	6.0	122	77
Georgia	2.8	9.3	232	90
Alabama	2.9	8.7	200	73
Tennessee	3.3	9.4	185	100
Oklahoma	3.3	11.5	248	101
New Mexico	3.6	7.0	94	83
Kentucky	3.6	9.4	161	97
Wyoming	3.6	12.0	233	109
West Virginia	3.7	10.9	195	96
North Dakota	4.1	8.2	100	81
Texas	4.1	10.7	161	108
Idaho	4.2	8.0	90	81
Delaware	4.5	18.2	304	127
Virginia	4.7	10.9	132	108
Iowa	4.7	12.2	160	122
Arizona	5.2	11.1	113	119
Indiana	5.3	13.5	155	121
Kansas	5.6	13.0	132	115
Colorado	5.6	11.5	105	175
Nebraska	5.7	11.8	107	124
Vermont	5.8	15.4	166	146
Utah	6.0	7.0	17	104
South Dakota	6.2	11.0	77	79
Nevada	6.3	18.7	197	151
Montana	6.4	13.9	117	96
Maine	6.4	12.6	97	117
Wisconsin	6.5	12.0	85	112
Florida	6.6	15.5	135	120
Michigan	6.6	14.5	120	121
Minnesota	6.6	12.3	86	126
Missouri	7.0	14.7	110	140
Oregon	7.2	13.9	93	134
Ohio	7.2	14.7	104	135
Louisiana	7.6	15.0	97	104
Washington	7.8	12.3	58	127
Pennsylvania	8.0	15.8	98	137
Maryland	9.3	16.5	77	164
Illinois	9.5	17.0	79	154
New Hampshire	9.8	13.9	42	133
California	10.0	15.0	50	172
Rhode Island	10.1	16.3	61	135
Massachusetts	10.5	16.4	56	183
Connecticut	10.7	18.3	71	152
New Jersey	11.5	21.0	83	140
New York	13.5	20.9	55	203

*In 1940.

nostic thoracotomy) and the more frequent use of radical surgery have uncovered many cases of respiratory cancer which would have been missed in earlier years. The growing tendency to obtain microscopic confirmation in suspected cases has had the same effect. The special morbidity studies conducted by the National Cancer Institute in ten large metropolitan areas showed that in 1938 some 66 per cent of the respiratory cancer cases diagnosed had been confirmed by biopsy or autopsy whereas by 1948 this proportion had risen to 75 per cent. Since the ten large metropolitan areas were well above the average as regards medical practice in 1938, it is likely that for the country as a whole the relative increase in biopsy and autopsy has been even greater.

4. The fact that the magnitude of the respiratory cancer death rates is clearly associated with the quantity and quality of medical facilities, and that during the 1940's respiratory cancer death rates increased most in states with low death rates and relatively low ratios of physicians to population, also supports the view that much of the increase in respiratory cancer was the result of improved diagnosis and more complete case finding.

5. The marked increase during the 1940's in the reported death rates from respiratory cancer among nonwhite lives can also be attributed largely to improved detection and better reporting of the disease in this segment of the population, particularly at the older ages. At these ages, some of the increase probably represents the reporting of respiratory cancer as the cause of death in cases in which the past would have been reported as due to senility or ill-defined causes.

6. The sharp declines in the mortality from tuberculosis, pneumonia, and other respiratory diseases, such as chronic bronchitis, have probably resulted in the detection of respiratory cancer cases which formerly would have been reported as deaths from these diseases. Since tuberculosis death rates have decreased least at the older ages, where respiratory cancer death rates have risen most, it is not likely that sizable numbers of deaths once reported as due to tuberculosis have come more recently to be reported as due

to respiratory cancer. It is likely, however, that the high death rates from pneumonia which prevailed before this disease came under control included many cases of respiratory cancer.

7. An increase in the proportion of cases where the respiratory system is reported as the sole or primary site rather than as the secondary site may be another factor in the recorded rise in respiratory cancer death rates. In this connection, it may be noted that in 1940 the number of deaths in the United States in which respiratory cancer was reported as an associated cause (7,375) was not much less than the number in which it was reported as the primary cause of death (9,543).

Other Factors in the Increase in Respiratory Cancer.—While it has been suggested that improved diagnosis, more complete case finding, and more accurate reporting of respiratory cancer have been responsible for most, if not all, of the increase in the reported incidence of the disease, many considerations do not support so extreme a view. On the whole, the evidence points to a real rise in the mortality from respiratory cancer.

The more significant of these considerations are:

1. During the past twenty-five years the white male mortality from respiratory cancer, adjusted for changes in age distribution, increased five times. An increase of this magnitude and rapidity appears greater than can be accounted for solely by better diagnosis, case finding, and reporting, especially as no other site of cancer has shown as large a proportionate increase. If all the increase in respiratory cancer were due to better detection, and reporting, it would mean that physicians practicing twenty-five years ago were able to identify at most only one out of five cases existing at that time—the increase is continuing despite the fact that the disease is now more generally recognized.

2. Among white females, mortality from respiratory cancer, adjusted for changes in age distribution, has only about doubled in the past twenty-five years. If all this increase were due to better detection and reporting, it would still be much smaller than the increase in white male mortality. This suggests that a considerable part of the increase in white male mortality from this disease cannot be accounted for in this manner, since it is difficult to see why physicians should be able to diagnose respiratory cancer more readily in one sex than in the other.

3. The magnitude of the increase in respiratory cancer death rates over the past twenty-five years has varied by age, being smallest at ages under 45, and greatest at the most advanced ages. If the increase at the younger ages were all due to better detection and reporting, it would still leave most of the increase at the older ages unaccounted for, since it is difficult to see why physicians should be able to diagnose respiratory cancer very much better at the older ages than at the younger ages.

4. The markedly higher death rates from respiratory cancer among white male Industrial policyholders as compared with those for white males in the general population cannot be explained in terms of the better diagnostic facilities in urban areas, since white female Industrial policyholders residing in the same areas show respiratory cancer death rates substantially the same as those for white females in the general population. The reasons for the higher death rates of white male Industrial policyholders must rather be sought in some environmental factors.

5. The lower death rates from respiratory cancer among white male Ordinary policyholders, who presumably have access to even better diagnostic facilities than Industrial policyholders or white males in the general population, also sug-

gest factors related to environment, occupation, and social class. The recent findings on the incidence of respiratory cancer in the two highest social classes in England and Wales point to the same conclusion. In this connection, it may be noted that several life insurance studies have indicated somewhat higher than average mortality from respiratory cancer in such numerically important occupations as painters, roofers and slaters, carpenters and cabinet makers, coppersmiths and tinsmiths, and electricians.

6. The geographic variations in respiratory cancer mortality in the general population likewise indicate that some environmental factors may be contributing to produce the higher death rates found in the most urbanized and industrial states. The high age-adjusted death rates in states such as Louisiana, Florida, and Nevada also appear to require explanation in terms of special factors.

7. There is reasonably convincing statistical evidence that a number of different factors may be implicated in the rise in the incidence of respiratory cancer. Adequate data are not available to show how much of the rise can be attributed to the effect of specific factors.

SUMMARY

The author presents statistical data, illustrated with charts and tables, on the death rates from cancer of the respiratory tract in the general population of the United States and among Industrial and Ordinary policyholders of the Metropolitan Life Insurance Company, comparing these rates with the death rates from other forms of cancer and correlating the evidence from the points of view of age, sex, race, region of residence, etc. Factors in the current increase of cancer of the respiratory tract are listed.

ZUSAMMENFASSUNG

Der Verfasser legt an Hand von Kurven und Tabellen statistische Angaben über die Sterblichkeitsziffern des Krebses der Atmungsorgane innerhalb der allgemeinen Bevölkerung der Vereinigten Staaten und unter den Industriellen und Sonstigen Versicherten der Metropolitan Life Insurance Company vor, vergleicht die Zahlen mit den Sterblichkeitsziffern bei anderen Arten des Krebses und betrachtet ihre Beziehungen zum Alter, Geschlecht und zur Rasse des Patienten, zur Gegend des Wohnsitzes usw. Die Kaktoren, die beim heutigen Anstieg der Häufigkeit des Krebses der Atmungsorgane eine Rolle spielen, werden angeführt.

RÉSUMÉ

L'auteur présente des dates statistiques, illustrées par cartes et courbes, sur la mortalité par les cancers des voies respiratoires parmi la population entière des États Unis et parmi la population, Industrielle et Ordinaire, assurée par la Métropolitan Life Insurance Comp. Il compare ces chiffres avec la mortalité par des autres formes de cancer, corrélativement d'après l'àge, sexe, région d'habitation etc. Des facteurs concernants l'augmentation présente des cas de cancer respiratoir sont régistrés.

RESUMEN

El autor presenta una estadística ilustrada con cuadros, sobre el grado de mortalidad del cáncer del aparato respiratorio en la población general de los Estados Unidos de América y entre los asegurados Industriales y Comunes de la Metropolitan Life Insurance Company, comparando este grado, con el grado de mortalidad de otros cánceres y relacionando la edad, sexo, raza, residencia, etc. Se ponen en unalista los factores que aumentan el cáncer del aparato respiratorio.

SUMARIO

O autor apresenta dados estatísticos, ilustrados com gráficos e quadros, sôbre a mortalidade por câncer do tracto respiratório na população geral dos Estados Unidos e entre assegurados Industriais e Comun da Metropolitan Life Insurance Company, comparando essas taxas com as devidas a outras formas de câncer e correlacionando os dados sob os aspectos idade, sexo, raça, região de residência, etc. São apresentados os fatores do aumento atual do câncer do tracto respiratório.

RIASSUNTO

L'utore presenta e documenta con grafici e tavole i dati statistici relativi alla mortalità per cancro del polmone sulla popolazione generale degli Stati Uniti e fra assicurati della Metropolitan Life Insurance Company, nel departimento Industriale ed Ordinario li paragona con quelli relativi alla mortalità per cancri di altre sedi, in rapporto all'età, al sesso, alla razza, alla provenienza ecc. Elenca, poi, i fattori responsabili dell'aumento dei carcinomi polmonari.

[illegible] to be eventual permanent vascular [illegible]. Repeated pregnancies and recurrent episodes [illegible] have some relationship to the later occurrence of hypertensive disease in that most women [illegible] permanent elevation of blood pressure did [illegible] pregnancies and at least two bouts of [illegible].

[illegible]

ACCIDENT PREVENTION IN CHILDHOOD—THE KEROSENE HAZARD

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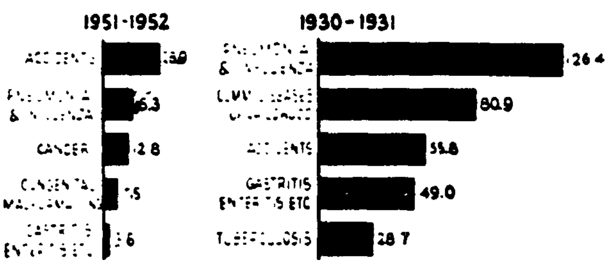
Accidents have become the leading cause of death among children over one year of age. The prominence of accident mortality is due in part to the widespread use of chemotherapeutic agents and immunization procedures, which have helped control communicable diseases and many other acute infections in childhood. Pneumonia, diarrhea, and enteritis—at one time the commonest causes of death among young children—have been gratifyingly controlled. In fact, pneumonia, diarrhea, measles, diphtheria, whooping cough, scarlet fever, meningitis, and poliomyelitis, all combined, do not kill as many American children as do accidents. One-third of all deaths in children at the present time result from accidents, while in 1900 accidents caused only one-twentieth of the deaths occurring in childhood.

There has been in recent years some reduction in deaths from accidents among children, but to a much less extent than from diseases (see figure). Since 1930 deaths from communicable diseases have been reduced 97%, from gastroenteritis 93%, from appendicitis 91%, from tuberculosis 89%, and from pneumonia and influenza 88%, but from accidents only 48%. This reduction in accidents does not necessarily mean, however, that children are being injured less frequently. Today physicians are saving more who have been burned, poisoned, crushed, or mangled. Over one-half of all fatal accidents in childhood occur among children under 5 years of age. Dietrich emphasized that the greatest efforts at accident prevention should be made in this age group, not only because these children have more accidents but because education for safety is more fruitful when directed toward young children. Accidents in the 1 to 4 year age group have risen in prominence as a cause of death. In 1930-1931 pneumonia, influenza, and the common communicable diseases of childhood ranked above accidents, with the gastrointestinal diseases not far behind. In 1951-1952 accidents were in first place, almost doubling in number the deaths from pneumonia and influenza, the next ranking group. This, however, is not the whole picture. It has been estimated by authorities on the accident problem that for every fatal accident among children there are at least 100 nonfatal accidents, 4 of which result in some permanent disability.

The table shows the distribution of the principal types of accidents among children aged 1 to 4 years. Although motor vehicles, burns, drowning, and falls all precede poisonings as causes of death, this cause nevertheless gives rise to an extremely important aspect of the problem and illustrates its magnitude. Poisonings are most likely to occur in children of ages 1 through 2 (see table). This is the age of inquisitiveness when some children will eat or drink almost anything.

KEROSENE POISONING

One of the commonest, though not most fatal, types of poisoning among young children is caused by the consumption of petroleum oils, principally kerosene. Bain in her study of accidental poisonings in children under 5 years of age in the United States found that petroleum products accounted for 25% of accidental poisonings in this age group. The Florida Children's



Leading causes of death in children aged 1 to 4 years. Death rates per 100,000. Cancer includes leukemia and Hodgkin's disease.

Commission in cooperation with the Florida chapter of the American Academy of Pediatrics and the Florida Pediatric Society recently sent a questionnaire to 156 hospitals in Florida in an effort to determine the incidence of poisonings within the state caused by ingestion of volatile oils. Of 90 hospitals returning the questionnaire, 79 accepted children who might be poisoned. In 1953, 229 children, all under 6 years of age, were admitted to 45 hospitals for treatment because of poisoning by volatile oils. Nearly all of these children were

Read before the Eighth Clinical Meeting of the American Medical Association, Miami, Fla., Dec. 1, 1954.

The statistics in the figure and table are based on experiences of the Metropolitan Life Insurance Company, Industrial Department.

1. Armstrong, D. B., and Cole, W. G.: Can Child Accidents Be Prevented in Your Community? Am. J. Pub. Health 39: [illegible] (May, pt. 1) [illegible].

2. Wheatley, G. M.: Accident Prevention and the General Practitioner, Postgrad. Med. 10: 442-445 (Nov.) 1951.

3. Dietrich, H. F.: Prevention of Childhood Accidents: What Are We Waiting For? J. A. M. A. 156: 929-931 (Nov. 6) 1954.

4. Footnotes 1 and 2.

5. Bain, K.: Death Due to Accidental Poisoning in Young Children, J. Pediat. 44: 616-623 (June) 1954.

API 06124

poisoned by drinking kerosene. In addition, 78 children were treated as outpatients in 18 hospitals, and it was estimated by 24 hospitals that 288 others probably were treated. Thus a total of over 500 Florida children were treated in that one year for volatile oil poisoning, caused in nearly all cases by ingestion of kerosene. There was only one death among this group. An examination of data from the bureau of vital statistics of the Florida State Board of Health, however, showed that four other children met death in the state in 1953 from drinking petroleum products. They were not treated in the reporting hospitals. These fatalities indicate, in all probability, a much larger incidence of this type of poisoning than was discovered as a result of the questionnaire.

A detailed study was made of all cases of poisoning from petroleum oil products recorded at one of the reporting hospitals, the Duval Medical Center, Jacksonville. During 1953, 76 patients were treated on the charity children's service, one of whom died. The mean

Percentage Distribution, by Principal Types, of Deaths from Accidents Among Children One to Four Years of Age—51-1952

Type of Accident	Age, Yr.				
	[illegible]	1	2	3	4
Accidents, total no. of deaths	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Death rate per [illegible]	[illegible]				
	% of Deaths				
Motor vehicle—total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Run over by motor vehicle	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Burns and conflagration—total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Conflagration	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Burns excluding conflagration	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hot liquids, steam, hot substances, etc.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Drowning	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Falls	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Poisoning by solids or liquids	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Choking by inhalation of food	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Absorption of poisonous gas	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Firearms	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
All other accidents, unspecified	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* Not available.

hospital stay of these children was 4.53 days. The per diem cost of patient care in this hospital in 1953 was $12.36. If, on the basis of this per diem cost and this average hospital stay, one computes the cost of hospitalizing the known 229 patients treated in Florida hospitals in 1953, he finds that hospitalization cost approximately $12,800. The cost in terms of psychological trauma to the young child and his parents, of course cannot be measured.

Kerosene ingestion is not a type of poisoning confined to the South, although it is probably commoner in this area than in other sections of the country. In June, 1953, the committee on accident prevention of the American Academy of Pediatrics reported a survey of 507 cases of accidental poisoning that occurred throughout the United States. In this series kerosene was the second commonest toxic agent, comprising 16% of the total.[6] A review of 375 cases of poisoning recorded in six Chicago hospitals during a recent nine month period, made by the poisoning control committee of the Illinois chapter of the American Academy of Pediatrics, disclosed that in 46 cases, or 12%, the cause of the poisoning was the ingestion of petroleum distillates, principally kerosene.[7]

In the Jacksonville area kerosene is widely used for heating homes as well as for cooking. Consequently, a decided rise in cases of poisoning during the winter months would be expected, but for many years there have been numerous cases in the wards during the summer. Throughout 1953, for example, the distribution of kerosene-poisoning cases at the Duval Medical Center was fairly equal, as shown in the following tabulation:

January	[illegible]	July	[illegible]
February	4	August	[illegible]
March	[illegible]	September	[illegible]
April	7	October	[illegible]
May	10	November	11
June	5	December	[illegible]

Although there may be more kerosene in the child's environment in the winter, it is during the summer that he will be more likely to drink it because of thirst. This observation emphasizes an important principle in the prevention among young children of poisoning from all toxic liquids: active youngsters should be given fluids between meals, especially in hot weather, so that thirst will not be the stimulus to the consumption of liquid poison.

It is not the purpose of this paper to present a complete discussion of kerosene poisoning. Certain controversial features of the disease, however, are reviewed here because they may have a bearing on survival. Deaths from kerosene poisoning may be due to two causes: (1) aspiration with pneumonitis, subsequent pulmonary edema, and secondary infection of the lungs, and (2) toxic effects on one or more organs or systems of the body, in particular the liver, stomach, and intestinal tract, and especially the brain. The lungs are almost invariably involved in severe cases, and it is now believed that aspiration is far more important than is absorption in causing damage to the lungs. In experimental animals pulmonary damage can be produced by the injection of kerosene intravenously. Some experimenters believe it also can be produced by injection of the oil into the gastrointestinal tract when the possibility of aspiration is removed.[8] Practically speaking, blood levels in man probably never would reach those produced in experimental animals when kerosene is injected intravenously. If there is pulmonary irritation from absorption alone, it is probably not great. Children who have consumed more than several ounces of kerosene quickly show signs of toxicity with drowsiness and later coma. Kerosene contains hydrocarbons commonly used in some anesthetics, but varies considerably in coma-producing ability because of variability in refining processes.

TREATMENT

The immediate problem facing all physicians treating children who have consumed kerosene is whether or not to aspirate the stomach. The condition of the child, and to a less extent the history, will serve as a practical guide

6. The Year Book of Pediatrics (1954-1955 Year Book Series), edited by George S. Siegel, Chicago, the Year Book Publishers, Inc., 1954, p. 367.

7. Poisoning Control Committee, Illinois Chapter of American Academy of Pediatrics: Personal communication to the author.

8. Bologna, N. A., and Woody, N. C.: Kerosene Poisoning, New Orleans M. & S. J. 101: 256-260 (Dec.), 1948.

in each individual case. If one can be sure only a small amount was swallowed, if vomiting has occurred, and if there are no signs of toxicity with drowsiness, the child is probably best left alone. On the other hand, if toxic signs, especially with dizziness, drowsiness, or coma, are present, or if someone actually saw him drink a considerable quantity, careful lavage of the stomach with the head and chest lowered, is indicated. Pinching off of the tube, quick withdrawal, and, if possible, avoidance of vomiting during lavage are important points in technique.

ACCIDENT PREVENTION

This brief report on poisoning from petroleum distillates in one state serves not only to illustrate the magnitude of the problem of poisoning among children but to stress particularly the importance of accidents, of all types, as a cause of morbidity and mortality among the young. No attempt has been made to discuss many important facets of the accident problem, such as accident proneness, for example. The fact that 20% of the accident victims, in some groups studied, sustained over 50% of the accidents is important to physicians. Accident repeaters should have a physical appraisal with special emphasis on vision, hearing, orthopedic status, and neurological integrity. Detailed psychological investigation may be necessary for those having no physical basis for repeated accidents.

All physicians who give medical care to children have an opportunity, indeed a responsibility, to promote accident prevention among them. General practitioners, who provide most of the medical care children receive, have especially good opportunities to promote safety. Becoming safety-minded and teaching safety to parents and children should entail little, if any, additional burden to the busy physician. Some specific suggestions of proved value in accident prevention that doctors can make a part of their routine practice are given below.

1. Education of parents in accident prevention should begin before the child learns to walk. Mention the common home accidents at well-child check-ups, whether in private office or clinic. Distribute pamphlets on accident prevention; they are available for the asking from several leading insurance companies and the National Safety Council. When such literature is left on waiting room tables, it does little good, but when given to a parent with firm instructions, "Read this," it can be of value. 2. On calls in the homes of children, observe unsafe conditions and suggest corrective measures. 3. When treating a patient for any accidental injury, inquire into the cause of the accident and tactfully point out how a recurrence can be prevented in the future. There is no better time than while treating an accidentally injured child to make the parents and the child himself aware that safety measures are of value. 4. In prescribing drugs, stress the dangers of injudicious use and careless storage. This is also a good time to inquire about the handling of harmful cleaning agents, insecticides, and fuel in the home. 5. When a child has repeated accidents, make a complete appraisal of the patient and his environment, in an attempt to find the cause. Public health nurses may be of value in such a study. 6. As a guardian of public health and well-being, be a leader in community projects directed toward safety and accident prevention.

2. [illegible]

CLINICAL NOTES

NEW METHOD FOR LOCAL ANESTHESIA IN PERORAL ENDOSCOPY

PRELIMINARY REPORT

Hubert J. Adler, M.D., Phoenix, Ariz.

Current methods of local anesthesia for peroral endoscopy are unsatisfactory because of (1) the toxic results of the effective surface anesthetics, (2) the discomfort—to put it mildly—to the patient caused by peroral endoscopies under local anesthesia, and (3) the lack of relaxation of the structures underlying the mucosa of the pharynx and larynx. A surface anesthetic does not relax the deeper structures such as the base of the tongue and the cricopharyngeus muscle (the "pinchcock of the esophagus"). The upper front teeth and their gums remain sensitive to the unavoidable pressure of the endoscope. The patient with long upper teeth and or a short, muscular neck is a dreaded prospect for peroral endoscopies.

I have devised a method whereby the conventional surface anesthetics can be avoided almost completely. The usual preoperative medication (barbiturates, narcotics, and atropine) is given. The area to be described below is anesthetized by injecting a procaine-hyaluronidase mixture (150 turbidity-reducing units to 30 cc. of 1% procaine) or a 2% lidocaine (Xylocaine) hydrochloride solution and by instilling a 5% hexylcaine (Cyclaine) hydrochloride—2% tripelennamine (Pyribenzamine) mixture (ratio of 3:1) into the tracheobronchial tree.

The superior laryngeal nerve is injected first. If one prefers the external approach, the space between the cranial border of the thyroid cartilage and the hyoid bone is palpated. A 1½ in. 23 gauge needle is inserted perpendicularly to the skin 0.5 cm. anteriorly to the superior cornu of the thyroid cartilage until a resistance (the thyrohyoid membrane) can be felt (see table, injection 1). Then the greater palatine canal is injected. The oral opening of this canal lies about 1 cm. medially to the second molar and 1 cm. anteriorly to the border between the hard and soft palate. It suffices to enter the greater palatine canal for a depth of 1.5 cm. This reaches the anterior, middle, and posterior palatine nerves, resulting in anesthesia of the hard and soft palate, uvula, and anterior pillars (see table, injection 2a). An alternate method is to inject the mucosa over-

From the Veterans Administration Hospital.

REPORT OF THE SUBCOMMITTEE ON CARCINOGENICITY

to the

API MEDICAL ADVISORY COMMITTEE

On Tuesday, October 25th, the Subcommittee on Carcinogenicity met in Dr. Eckardt's room in the Terrace Plaza Hotel in Cincinnati. The meeting got under way about 9:00 with the following members in attendance: Dr. M. N. Newquist, Dr. E. K. Linder, Dr. R. C. Mithoff, Dr. E. W. Adams, Dr. M. M. Marisic, and Dr. R. E. Eckardt. The reports by Dr. Horton and Dr. Phair were discussed. At about 10:30 the group moved to the Kettering Laboratory and conducted their meeting in the presence of Dr. Kehoe, Dr. Horton, Dr. Phair, and Dr. Heyroth of the Kettering Laboratory. In addition, Dr. B. E. Bennison of the Medical Research Division of Esso Research and Engineering Company sat in as a guest.

Distributed to all members of the Medical Advisory Committee prior to the San Francisco meeting are reports by Dr. Horton and Dr. Phair dated October 1955 and summarizing all the work which has been done on this project to date. In addition data tables of Dr. Horton's work will have been distributed to the members of the Medical Advisory Committee by the time of the San Francisco meeting.

In Table 1 of these summary tables, which is seventeen pages long, the data on various fractions from the refining of petroleum have been collected. Included in the Table besides the relative carcinogenic potency is a column listing the benzpyrene content of the oil sample as determined by the method Dr. Horton had published in the scientific literature. In general it can be said that particularly for severely cracked materials the relative carcinogenic potency at least roughly follows the benzpyrene content of the oil. There are however certain samples, in particular lubricants and uncracked stocks, which show a much greater carcinogenic potency for the mouse than would be anticipated from the benzpyrene content. It was this observation which led the Kettering Laboratory to the theory that certain materials serve as accelerators to the carcinogenic action of polycyclic aromatic hydrocarbons. As a result of this theory the laboratory is now tentatively expressing its concept of carcinogenic potency in the following formula:

$$P_{MC} = M_a (C_1 + C_2 + C_3)$$

In this summary the various terms are defined as below:

P_{MC} is equal to the carcinogenic potency for mice exhibited by an oil, expressed in terms of the concentration of methylcholanthrene in benzene that produces tumors in the skin of mice at the same rate and under comparable experimental conditions as that produced by the oil.

M_a equals the contribution to potency due to accelerators.

C_1 equals the benzpyrene type polycyclic carcinogens expressed in methylcholanthrene equivalents.

C_2 equals the carcinogenic substances extractable by maleic anhydride (probably derivatives of benzanthracene) expressed in methylcholanthrene equivalents.

C_3 equals carcinogenic substances insoluble in concentrated sulfuric acid expressed in methylcholanthrene equivalents.

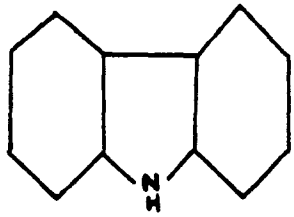
Chromatography will presumably separate a given oil into two components, the first of which will represent the M_a in the above equation and the remainder of which will represent the $(C_1 + C_2 + C_3)$. Thus by chromatographing a series of oils in which the P_{MC} is known (as shown in Table 1, last column) it should be possible to solve the above equation for M_a since the $(C_1 + C_2 + C_3)$ portion of the equation will be retained on the chromatograph column and can be elutriated as a group free of the M_a component. This work naturally will be principally devoted to a study of the differences between uncracked stocks since it is in these uncracked stocks that the M_a appears to have the greatest significance. In fact, the laboratory has developed some evidence, as indicated in Table 6 of their most recent tabulation summary, that the M_a factor may vary from one to six or possibly even more.

The laboratory has begun to use benzpyrene as a reference carcinogen since it has been the feeling of the Subcommittee and the laboratory that benzpyrene might be a more representative carcinogen for petroleum products than methylcholanthrene. The data collected by the laboratory and summarized in Table 4 suggest that benzpyrene at a given concentration has only about 50% of the activity that the same concentration of methylcholanthrene has. This fact should be kept in mind in attempting to interpret any experimental work which the laboratory is doing in which the benzpyrene is used as a carcinogen.

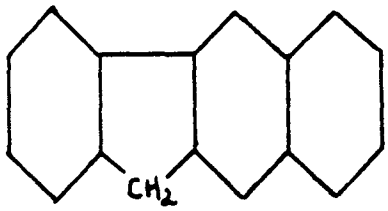
The laboratory has undertaken some work on the possible inhibiting effect of one carcinogen upon another and believes that all published data claiming to show inhibition of one carcinogen by another are subject to the error of poor health of the animals due to high concentrations of mixtures of the two carcinogens. The experimental data in support of this concept are presented in Table 5.

In Table 7 data are presented by the laboratory on solutions of benzpyrene in various solvents which suggest that many of the solvents have a significant accelerating action of benzpyrene much as they did upon methylcholanthrene. For instance, this accelerating effect seems to have made itself evident in paraffins, olefins, cycloparaffins, alkyl benzenes, and alkyl naphthalenes, particularly when these materials exceeded a certain chain length. Other experiments which have been conducted by the laboratory are summarized in Tables 8, 9, 10, and 11 and the washing experiments are summarized in Table 12, which contains three pages.

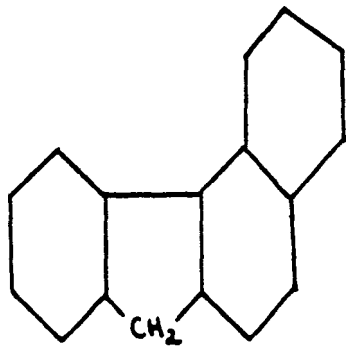
The laboratory is now collecting evidence which suggests that the aromatics of oils of the nature of API-8 contain about 15-20% of non-hydrocarbons. These non-hydrocarbons seem to be of the carbazole type. For instance, the laboratory has isolated from API-8 (Table 1 page 13) and other higher fractions of this series the components carbazole which has the formula below.



In addition to this type compound the laboratory has isolated compounds of the 1,2-benzfluorine class and of the 2,3-benzfluorine class.



2,3-benzfluorine



1,2-benzfluorine

It is important to emphasize that though structurally these two classes of compounds appear quite similar, nonetheless chemically they are quite different.

In addition to this chemical work the laboratory is pursuing its attempt to isolate what it calls a low boiling carcinogen which presumably boils in the range of 720-750°F. It does not believe that carbazole or the benzfluorines are this carcinogen but it does believe that evidence has accumulated to suggest that there must be such a carcinogen so that isolating it may be of help in solving some of the problems now facing the laboratory in its solution of the problems of the carcinogenicity of this type oil.

It is the belief of the laboratory that when they have obtained an ultimate solution to the equation

$$P_{MC} = M_a (C_1 + C_2 + C_3)$$

that it will then be possible to present to the petroleum industry an analytical tool which will permit the evaluation of the potential relative carcinogenicity of any petroleum material. It should be recognized however that this method will probably be long and tedious and require the determination of at least four components and therefore may not be particularly

practical for use in refinery operations. However, this bridge presumably can only be crossed when we come to it. At the present time the laboratory estimates that it will take six generations of mice at a minimum to obtain the necessary answers to the above equation. With a minimum life of nine months for each generation and assuming that each step proceeds without any hitch, this represents a minimum of fifty-four months of additional work by the laboratory in the solution of this problem.

The report by Dr. Phair shows encouraging results in attempts at making statistical evaluations of cancer in the various participating companies. It is, however, discouraging to realize that only sixteen of twenty-five companies have participated in this effort and that in the last few years the number of participants may have diminished even more than this. For instance, in 1954 only twelve companies participated in the epidemiological studies. It should be quite apparent to the medical members of the Medical Advisory Committee that if there is any hope of accomplishing anything with these epidemiological studies this hope resides in the full cooperation of all of the participating companies. This would then provide a large enough sample so that significant statistical analysis could be made and leads shown which might permit more detailed studies by individual companies or by the group as a whole. Nonetheless it must be recognized that if participation does not continue in this project it is doomed to failure through no fault of Dr. Phair, but strictly due to the failure of cooperation the part of the participating companies and their medical directors on the Medical Advisory Committee. Since the Subcommittee has been emphasizing the epidemiological aspects on this problem so long and intends to push the epidemiological studies, even at the expense of the experimental studies, it therefore seems apparent that if we are unable to obtain cooperation the epidemiological studies might just as well be terminated. The Subcommittee is in no position to do anything but make suggestions to the individual medical directors who sit in on the Medical Advisory Committee, but it is the suggestion of this Subcommittee that the experimental work in and of itself has no real value since it has no direct tie in with the human experience. The whole meat of all of the work which has been sponsored by the Subcommittee on Carcinogenicity lies in an attempt to develop an understanding of things that may be of importance to man and if the studies on man, namely the epidemiological studies, are not successful then all of the work of the Subcommittee will have been in vain. The Subcommittee simply wishes to re-emphasize that for the past five or six years it has been stressing and encouraging all medical directors to participate in the epidemiological studies.

REE/jbm
October 31, 1955

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CHIEF CLINICAL RESEARCH PHYSICIAN

November 2, 1955

Mr. D. V. Stroop
American Petroleum Industry
50 W. 50th Street
New York 20, N. Y.

Dear Mr. Stroop:

I am attaching some information recently received from Dr. Newquist who received it from our British associates in the field of petroleum cancer studies. I believe that the members of the Medical Advisory Committee as well as those at the Kettering Laboratory would be interested in reviewing the Progress Report by Dr. Carruthers and Dr. Cook, and also Progress Report by Dr. Woodhouse and Dr. Squire. I would appreciate it if you would have these reports duplicated for these individuals. I do not believe that the rest of the attached information would be worthwhile duplicating since it concerns only the agenda and minor changes in the nomenclature.

Very truly yours,

R. E. Eckardt

R. E. ECKARDT, M. D.

REE:evn

Encs.
MRC.55/830
MRC.55/815
MRC.55/814
MRC.55/804

Copy From D. V. Stroop For Information of Members of Medical Advisory Committee
11/4/55

MEDICAL RESEARCH COUNCIL

"Unclassified"
For Restricted Circulation
(Members of Committee)

MRC.55/830
CMO. Ag.19

Committee on the Carcinogenic Action of Mineral Oils

AGENDA

for the Nineteenth Meeting to be held at
26, Old Queen Street, Westminster, London, S.W.1.,
on Tuesday, 25th October, 1955, at 11.15 a.m.

Minutes of the previous meeting (MRC.55/510, CMO. Min.18 - already circulated)

2. Amendments to nomenclature of oil fractions.
A memorandum (MRC.55/815, CMO.55/8) (Enclosure A)

3. Expenses grant to Dr. William E. Smith for testing oil fractions (Minute 155)

4. Progress Reports

(i) Chemical - by W. Carruthers and J.J. Cook (MRC.55/814, CMO.55/9 - (Enclosure B)

(ii) Biological - by D.L. Woodhouse and J.R. Squire.
Progress Report No. XV (MRC.55/804, CMO.55/7 - (Enclosure C)

5. Future Plans

6. Any other business

7. Date of next meeting

MEDICAL RESEARCH COUNCIL

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(Members of Committee)

MRC.55/815
CMMO.55/8

Committee on the Carcinogenic Action of Mineral Oils

Nomenclature of Oil Fractions

It will be recalled that, at the Eighteenth Meeting of the Committee, the standardisation of the nomenclature of the various oil fractions was discussed (Minute 152) and it was agreed that Professor Squire and Professor Morton should consider this in the light of coding symbols already agreed (Minute 136).

Professor Squire and Professor Morton now propose the following amendment to Minute 136.

paragraph 4, line 7:

DELETE "..... were split into aromatic (A) and raffinate (R) portions."
SUBSTITUTE "..... were split into aromatic (A) and paraffin raffinate (P) portions."

This amendment and the previous confusion of symbols call for amendments in the following documents as shown:

CMMO.55/2 and CMMO 55/6: for R read P
CMMO.54/16; CMMO.55/3 and CMMO.55/4; for M, P and R read m, p and r.

MEDICAL RESEARCH COUNCIL

"Unclassified"
For Restricted Circulation
(Members of Committee)

MRC.55/814
CAMO.55/9

Committee on the Carcinogenic Action of Mineral Oils

Progress Report
by
J. Carruthers and J.W. Cook

The 1955-56 series of animal experiments with the Kuwait fractions are to be carried out with fractions obtained from the active non-picrate-forming material by chromatography and fractional distillation. For this purpose, the five non-picrate-forming fractions K_4S_6bAr, K_4S_7aAr, K_4S_7bAr, K_4S_8aAr, and K_4S_8bAr have been separated into three main fractions by chromatography on alumina by the general method outlined in the last Report. The oil fractions, in batches of about 200 g., were adsorbed on 2 Kg. of freshly activated alumina and successively eluted with petroleum ether, benzene and methanol. Elution with each solvent was continued until no more material was recovered, and three fairly well defined fractions obtained. Corresponding eluates from all the chromatograms were combined, and the three composite fractions sent to Professor Morton for fractional distillation. The total quantities of these fractions obtained were as follows:-

(i) petroleum ether eluate; 1977 g. (77%) yellow oil,

(ii) benzene eluate; 349 g. (13.5%) orange-yellow oil,

(iii) methanol eluate; 244 g. (9.5%) black viscous gum with a strong unpleasant smell.

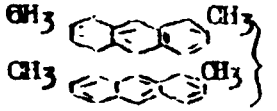
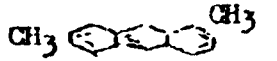
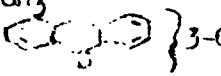
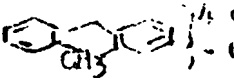
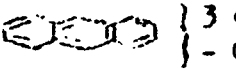
The ultra-violet absorption spectra of the chromatogram fractions K_4S_7aAr i, ii and iii, and K_4S_7bAr i, ii and iii, indicate that fractions i and ii are still complex mixtures of different ring systems. In each case there is general absorption with a fall of intensity toward the long wavelength. The spectra of the petroleum ether eluates (i) however, show two well defined maxima at 234 and 326 mμ which possibly indicate the presence of considerable amounts of dibenzothiophen derivatives in these fractions. Experiments are in progress which may lead to a decision on this point. In contrast to these, the spectra of the methanol eluates (iii) exhibited well defined maxima at 243, 292 and 318-355 mμ. (log E 1/cm; 4.9, 4.3, 4.9, and 5.0, 4.5, 4.9) attributable to the presence of carbazole derivatives. This is quite in keeping with the difficulty of removing this material from the chromatogram. It is of interest in this connection that at least one carbazole

[illegible] isolated from a corresponding fraction in the picrate-forming [illegible].

We are continuing our work with the picrate-forming fractions (g). These have also been subdivided by large-scale chromatography, and we have isolated two other compounds from them. One of these, from K_4Sraalp(i) had m.p. 64-66° and was shown by its elementary analysis and ultra-violet absorption spectrum to be a trimethyl [illegible] $C_{14}H_{12}S$. Our [illegible] attempts to desulphurise this compound with Raney nickel in boiling [illegible] were unsuccessful. In tetrahydrofurfuryl alcohol desulphurisation was achieved but was accompanied by hydrogenation with formation of a more or less completely hydrogenated diphenyl derivative which has not yet been identified. The second compound, isolated from $K_4$3-alp(i) had m.p. 100° and was shown to be a derivative of phenanthrene by its ultra-violet absorption spectrum. Elementary analyses of the substance and its s-trinitrobenzene complex (m.p. 205-206°) indicated the molecular formula $C_{15}H_{18}$ for the parent hydrocarbon. The melting points of these two compounds, however, do not correspond to those recorded for any known $C_{15}H_{18}$ phenanthrene hydrocarbon or its trinitrobenzene complex.

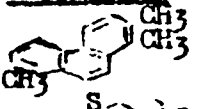
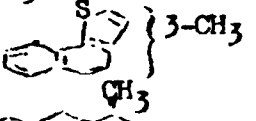
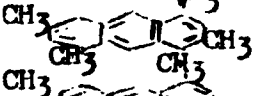
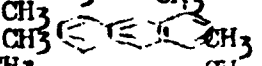
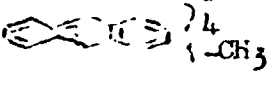
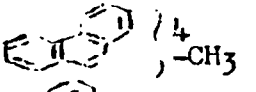
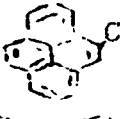
In response to a request by the Committee the following Table has been drawn up delineating the compounds which have so far been isolated from the Kuwait oil.

Compound isolated		Molecular Formula
Eutectic of 2:6- and 2:7-dimethylanthracene		$C_{16}H_{14}$
2:6-Dimethylanthracene		$C_{16}H_{14}$
2:7-Dimethylanthracene		$C_{16}H_{14}$
1:8-Dimethylphenanthrene		$C_{16}H_{14}$
Unknown trimethyldibenzthiophen (or equivalent) (m.p. 84-86°).		$C_{15}H_{14}S$
Unknown tetra- or pentamethyl-fluorene (or equivalent) (m.p. 198-199°)	or	$C_{17}H_{18}$ $C_{18}H_{20}$
2:3:6-Trimethylanthracene		$C_{17}H_{16}$
Unknown tri- or tetramethyl-anthracene (m.p. 108-110°).	or	$C_{17}H_{16}$ $C_{18}H_{18}$
Unknown tri- or tetramethyl-anthracene (m.p. 224-225°)	or	$C_{17}H_{16}$ $C_{18}H_{18}$
Unknown tri- or tetramethyl-anthracene (m.p. 169-170°)	or	$C_{17}H_{16}$ $C_{18}H_{18}$

Molecular Weight	Structural Formula	Fraction from which isolated
206		K_4S_1aAm, K_4S_1bAm, K_4S_2aAm.
206		K_4S_2aAm.
206		K_4S_2bAm.
206		K_4S_2bAp.
226	 3-CH_3	K_4S_2bAp.
222 or 236	 4 or 5 - CH_3	K_4S_2bAp.
220		K_4S_3aAm, K_4S_4aAm, K_4S_5bAm, K_4S_6bAm, K_4S_5bAm, K_4S_6bAm.
220 or 234	 3 or 4 - CH_3	K_4S_3bAm.
220 or 234	 3 or 4 - CH_3	K_4S_5bAm, K_4S_6bAm.
220 or 234	 3 or 4 - CH_3	K_4S_6bAm

Compound isolated	Molecular Formula
1:2:8-Trimethylphenanthrene	$C_{17}H_{16}$
Unknown trimethyl-6:7-benzothionaphthen	$C_{15}H_{14}S$
1:3:5:7-Tetramethylanthracene	$C_{18}H_{18}$
1:3:6:7-Tetramethylanthracene	$C_{18}H_{18}$
2:3:6:7-Tetramethylanthracene	$C_{18}H_{18}$
Unknown tetramethylanthracene (m.p. 67-69°)	$C_{18}H_{18}$
Unknown tetramethylphenanthrene (m.p. 100°)	$C_{18}H_{18}$
1-Methylpyrene	$C_{17}H_{12}$
Unknown tetra- or penta-methylcarbazole (m.p. 184-185°)	$C_{16}H_{17}N$ or $C_{17}H_{19}N$

10th October, 1955.

Molecular Weight	Structural Formula	Fraction from which isolated.
220		K_4S_6 b.p.
226		K_4S_6 b.p.
234		K_4S_7 a.m., K_4S_7 b.m.
234		K_4S_8 a.m., K_4S_8 b.m.
234		K_4S_8 a.m., K_4S_8 b.m.
234		K_4S_7 b.m., K_4S_8 a.m.
234		K_4S_7 b.p.
216		K_4S_7 a.p.
223 or 237		K_4S_7 a.p.

MEDICAL RESEARCH COUNCIL

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MRC.55/804
CAN'O. 55/7

COMMITTEE ON THE CARCINOGENIC ACTION OF NEUTRAL OILS

Progress Report No.XV (Sept. 1955)

From D.L. Woodhouse and J.M. Squire, Cancer Research Laboratories, and Department of Pathology, University of Birmingham, Medical School.

Tests carried out by D.L. Woodhouse (1954-55)

The fractions have been applied to the rabbits for 45 weeks and to the mice for 40 weeks. The rabbit tumours are given in Table I.

TABLE I

Rabbit tumours at 45 weeks

Fraction		tumours	Fraction		tumours	Fraction		tumours
$K_4S_4A_m$	(j)	0	$K_4S_4A_p$	(t)	1	$K_4S_4A_r$	(p)	4
$K_4S_5A_m$	(n)	0	$K_4S_5A_p$	(d)	2	$K_4S_5A_r$	(r)	2
$K_4S_6A_am$	(f)	0	$K_4S_6A_ap$	(g)	8	$K_4S_6A_ar$	(b)	5
$K_4S_6A_bm$	(m)	1	$K_4S_6A_bp$	(c)	1	$K_4S_6A_br$	(c)	7
$K_4S_7A_m$	(o)	1	$K_4S_7A_p$	(h)	2	$K_4S_7A_r$	(k)	4
$K_4S_8A_m$	(a)	0	$K_4S_8A_p$	(q)	2	$K_4S_8A_r$	(s)	3
Total		2			16			25
K_4S_9	(l)	8	D(2)	(u)	15	D($\frac{1}{2}$)	(i)	7

Mouse tumours have appeared in the following mineral oil fractions. b (1); c (1); k (1); l (2); m (1); p (1):

Mice treated with the weaker standard D($\frac{1}{2}$) had 100% incidence of tumours by the 28th week. The stronger standard D(2) had produced 100% of tumours at the end of 15 weeks.

A complete return of all tumours with sites will be given on completion of the experiments, i.e. after 92 weeks.

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P. O BOX 51, LINDEN, N. J.

MEDICAL RESEARCH DIVISION
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NATHAN V HENDRICKS, CH E
HEAD INDUSTRIAL HYGIENIST
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HEAD TOXICOLOGIST
BERTRAND E BENNISON M D.
CHIEF CLINICAL RESEARCH PHYSICIAN

November 2, 1955

Mr. D. V. Stroop
American Petroleum Industry
50 W. 50th Street
New York 20, N. Y.

Dear Mr. Stroop:

I am attaching some information recently received from Dr. Newquist who received it from our British associates in the field of petroleum cancer studies. I believe that the members of the Medical Advisory Committee as well as those at the Kettering Laboratory would be interested in reviewing the Progress Report by Dr. Carruthers and Dr. Cook, and also Progress Report by Dr. Woodhouse and Dr. Squire. I would appreciate it if you would have these reports duplicated for these individuals. I do not believe that the rest of the attached information would be worthwhile duplicating since it concerns only the agenda and minor changes in the nomenclature.

Very truly yours,

R. E. Eckardt

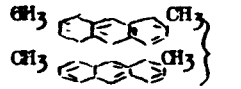
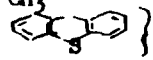
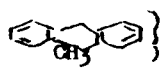
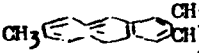
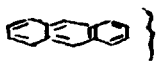
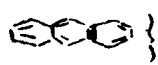
R. E. ECKARDT, M. D.

REE:evn

Encs.
MRC.55/830
MRC.55/815
MRC.55/814
MRC.55/804

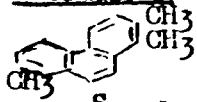
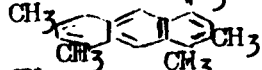
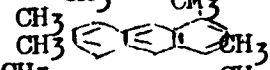
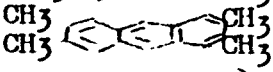
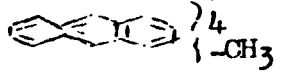
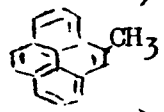
Copy From D. V. Stroop For Information
of Members of Medical Advisory Committee
11/4/55

Compound isolated	Molecular Formula
Eutectic of 2:6- and 2:7-dimethylanthracene	$C_{16}H_{14}$
2:6-Dimethylanthracene	$C_{16}H_{14}$
2:7-Dimethylanthracene	$C_{16}H_{14}$
1:8-Dimethylphenanthrene	$C_{16}H_{14}$
Unknown trimethyldibenzthiophen (or equivalent) (m.p. 84-86°).	$C_{15}H_{14}S$
Unknown tetra- or pentamethyl-fluorene (or equivalent) (m.p. 198-199°)	$C_{17}H_{18}$ or $C_{18}H_{20}$
2:3:6-Trimethylanthracene	$C_{17}H_{16}$
Unknown tri- or tetramethyl-anthracene (m.p. 108-110°).	$C_{17}H_{16}$ or $C_{18}H_{18}$
Unknown tri- or tetramethyl-anthracene (m.p. 224-225°)	$C_{17}H_{16}$ or $C_{18}H_{18}$
Unknown tri- or tetramethyl-anthracene (m.p. 169-170°)	$C_{17}H_{16}$ or $C_{18}H_{18}$

Molecular Weight	Structural Formula	Fraction from which isolated
206		K_4S_1aAm, K_4S_1bAm, K_4S_2aAm.
206		K_4S_2aAm.
206		K_4S_2bAm.
206		K_4S_2bAp.
226	 3-CH_3	K_4S_2bAp.
222 or 236	 4 or 5 - CH_3	K_4S_2bAp.
220		K_4S_3aAm, K_4S_4aAm, K_4S_3bAm, K_4S_4bAm, K_4S_6aAm, K_4S_6bAm.
220 or 234	 3 or 4 - CH_3	K_4S_5bAm.
220 or 234	 3 or 4 - CH_3	K_4S_5bAm, K_4S_6bAm.
220 or 234	 3 or 4 - CH_3	K_4S_6bAm

Compound isolated	Molecular Formula
1:2:8-Trimethylphenanthrene	$C_{17}H_{16}$
Unknown trimethyl-6:7-benzothionaphthen	$C_{15}H_{14}S$
1:3:5:7-Tetramethylanthracene	$C_{18}H_{18}$
1:3:6:7-Tetramethylanthracene	$C_{18}H_{18}$
2:3:6:7-Tetramethylanthracene	$C_{18}H_{18}$
Unknown tetramethylanthracene (m.p. 67-69°)	$C_{18}H_{18}$
Unknown tetramethylphenanthrene (m.p. 100°)	$C_{18}H_{18}$
1-Methylpyrene	$C_{17}H_{12}$
Unknown tetra- or penta-methylcarbazole (m.p. 184-185°) or	$C_{16}H_{17}N$
	$C_{17}H_{19}N$

10th October, 1955.

Molecular Weight	Structural Formula	Fraction from which isolated.
220		$K_4S_6bAp.$
226		$K_4S_6bAp.$
234		K_4S_7aAm, $K_4S_7bAm.$
234		K_4S_8aAm, $K_4S_8bAm.$
234		K_4S_8aAm, $K_4S_8bAm.$
234		K_4S_7bAm, $K_4S_8aAm.$
234		$K_4S_7aAp.$
216		$K_4S_7aAp.$
223 or 237		$K_4S_7aAp.$

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MRC.55/804
CANCO. 55/7

COMMITTEE ON THE CARCINOGENIC ACTION OF MINERAL OILS

Progress Report No.XV (Sept. 1955)

From D.L. Woodhouse and J.R. Squire, Cancer Research Laboratories, and Department of Pathology, University of Birmingham, Medical School.

Tests carried out by D.L. Woodhouse (1954-55)

The fractions have been applied to the rabbits for 45 weeks and to the mice for 40 weeks. The rabbit tumours are given in Table I.

TABLE I

Rabbit tumours at 45 weeks

Fraction		tumours	Fraction		tumours	Fraction		tumours
$K_4S_4A_m$	(j)	0	$K_4S_4A_p$	(t)	1	$K_4S_4A_r$	(p)	4
$K_4S_5A_m$	(n)	0	$K_4S_5A_p$	(d)	2	$K_4S_5A_r$	(r)	2
$K_4S_6A_am$	(f)	0	$K_4S_6A_ap$	(g)	8	$K_4S_6A_ar$	(b)	5
$K_4S_6A_bm$	(m)	1	$K_4S_6A_bp$	(c)	1	$K_4S_6A_br$	(c)	7
$K_4S_7A_m$	(o)	1	$K_4S_7A_p$	(h)	2	$K_4S_7A_r$	(k)	4
$K_4S_8A_m$	(a)	0	$K_4S_8A_p$	(q)	2	$K_4S_8A_r$	(s)	3
Total		2			16			25
K_4S_9	(l)	8	D(2)	(u)	15	D($\frac{1}{2}$)	(i)	7

Mouse tumours have appeared in the following mineral oil fractions. b (1); c (1); k (1); l (2); m (1); p (1):

Mice treated with the weaker standard D($\frac{1}{2}$) had 100% incidence of tumours by the 28th week. The stronger standard D(2) had produced 100% of tumours at the end of 15 weeks.

A complete return of all tumours with sites will be given on completion of the experiments, i.e. after 52 weeks.

MEDICAL RESEARCH COUNCIL

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MRC.55/814
CAMO.55/9

Committee on the Carcinogenic Action of Mineral Oils

Progress Report
by
W. Carruthers and J.W. Cook

The 1955-56 series of animal experiments with the Kuwait fractions are to be carried out with fractions obtained from the active non-picrate-forming material by chromatography and fractional distillation. For this purpose, the five non-picrate-forming fractions K_4S_6bhr, K_4S_7air, K_4S_7bhr, K_4S_8ahr, and K_4S_8bhr have been separated into three main fractions by chromatography on alumina by the general method outlined in the last Report. The oil fractions, in batches of about 200 g., were adsorbed on 2 Kg. of freshly activated alumina and successively eluted with petroleum ether, benzene and methanol. Elution with each solvent was continued until no more material was recovered, and three fairly well defined fractions obtained. Corresponding eluates from all the chromatograms were combined, and the three composite fractions sent to Professor Morton for fractional distillation. The total quantities of these fractions obtained were as follows:-

(i) petroleum ether eluate; 1977 g. (77%) yellow oil,

(ii) benzene eluate; 349 g. (13.5%) orange-yellow oil,

(iii) methanol eluate; 244 g. (9.5%) black viscous gum with a strong unpleasant smell.

The ultra-violet absorption spectra of the chromatogram fractions K_4S_7ahr i, ii and iii, and K_4S_7bhr i, ii and iii, indicate that fractions i and ii are still complex mixtures of different ring systems. In each case there is general absorption with a fall of intensity toward the long wavelength. The spectra of the petroleum ether eluates (i) however, show two well defined maxima at 234 and 328 mμ which possibly indicate the presence of considerable amounts of dibenzothiophen derivatives in these fractions. Experiments are in progress which may lead to a decision on this point. In contrast to these, the spectra of the methanol eluates (iii) exhibited well defined maxima at 243, 292 and 318-355 mμ, (log E 1/cm; 4.9, 4.3; 3.9, and 5.0, 4.5, 4.07 attributable to the presence of carbazole derivatives. This is quite in keeping with the difficulty of removing this material from the chromatogram. It is of interest in this connection that at least one carbazole

homologue has been isolated from a corresponding fraction in the picrate-forming series.

We are continuing our work with the picrate-forming fractions (p). These have also been subdivided by large-scale chromatography, and we have isolated two other compounds from them. One of these, from K_4S_2alp(i) had m.p. 84-86° and was shown by its elementary analysis and ultra-violet absorption spectrum to be a trimethyldibenzothiophen $C_{15}H_{14}S$ or its equivalent. Attempts to desulphurise this compound with Raney nickel in boiling ethanol were unsuccessful. In tetrahydrofurfuryl alcohol desulphurisation was achieved but was accompanied by hydrogenation with formation of a more or less completely hydrogenated diphenyl derivative which has not yet been identified. The second compound, isolated from K_4S_7alp(i) had m.p. 100° and was shown to be a derivative of phenanthrene by its ultra-violet absorption spectrum. Elementary analyses of the substance and its s-trinitrobenzene complex (m.p. 205-206°) indicated the molecular formula $C_{18}H_{18}$ for the parent hydrocarbon. The melting points of these two compounds, however, do not correspond to those recorded for any known $C_{18}H_{18}$ phenanthrene hydrocarbon or its trinitrobenzene complex.

In response to a request by the Committee the following Table has been drawn up delineating the compounds which have so far been isolated from the Kuwait oil.

MEDICAL RESEARCH COUNCIL

"Unclassified"
For Specified Circulation
(Members of Committee)

MRC.55/830
CAMO. Ag.19

Committee on the Carcinogenic Action of Mineral Oils

AGENDA

for the Nineteenth Meeting to be held at
26, Old Queen Street, Westminster, London, S.W.1.,
on Tuesday, 25th October, 1955, at 11.15 a.m.

1. Minutes of the previous meeting (MRC.55/510, CAMO. Min.18 - already circulated)

2. Amendments to nomenclature of oil fractions.
A memorandum (MRC.55/815, CAMO.55/8) (Enclosure A)

3. Expenses grant to Dr. William E. Smith for testing oil fractions (Minute 155)

4. Progress Reports

   (i) Chemical - by W. Carruthers and J.W. Cook (MRC.55/814, CAMO.55/9 - (Enclosure B)

   (ii) Biological - by D.L. Woodhouse and J.R. Squire.
   Progress Report No. XV (MRC.55/804, CAMO.55/7 -(Enclosure C)

5. Future Plans

6. Any other business

7. Date of next meeting

MEDICAL RESEARCH COUNCIL

"Unclassified"
For Specified Circulation
(Members of Committee)

MRC.55/815
CAMO.55/8

Committee on the Carcinogenic Action of Mineral Oils

Nomenclature of Oil Fractions

It will be recalled that, at the Eighteenth Meeting of the Committee, the standardisation of the nomenclature of the various oil fractions was discussed (Minute 152) and it was agreed that Professor Squire and Professor Morton should consider this in the light of coding symbols already agreed (Minute 136).

Professor Squire and Professor Morton now propose the following amendment to Minute 136.

paragraph 4, line 7:

DELETE "..... were split into aromatic (A) and raffinate (R) portions."
SUBSTITUTE "..... were split into aromatic (A) and paraffin raffinate (P) portions."

This amendment and the previous confusion of symbols call for amendments in the following documents as shown:

CAMO.55/2 and CAMO 55/6: for R read P
CAMO.54/16; CAMO.55/3 and CAMO.55/4; for M, P and R read m, p and r.

API 06150

ESSO RESEARCH AND ENGINEERING COMPANY

(FORMERLY STANDARD OIL DEVELOPMENT COMPANY)

P O BOX 51, LINDEN, N. J.

MEDICAL RESEARCH DIVISION

ROBERT E. ECKARDT, PH.D., M.D.
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HEAD TOXICOLOGIST

BERTRAND E. BENNISON, M.D
CHIEF CLINICAL RESEARCH PHYSICIAN

November 15, 1955

Mr. D. V. Stroop
American Petroleum Institute
50 West 50th Street
New York 20, New York

Dear Mr. Stroop:

Enclosed is copy of the Minutes of the Meeting of Research No. 2 Committee of the Institute of Petroleum, and copy of the Progress Report of the Committee on the Carcinogenic Action of Mineral Oils of the Medical Research Council. Please have these duplicated for distribution to members of the Subcommittee on Carcinogenicity of the API, and to the interested individuals at the Kettering Laboratory.

Very truly yours,

R. E. Eckardt/mak

R. E. ECKARDT, M. D.

REE:mak

Encs. 2

Copy From D. V. Stroop For Information
Of Members Of Medical Advisory Committee
11/17/55

MEDICAL RESEARCH COUNCIL

"Unclassified"
For Specified Circulation
(Members of Committee)

MRC.55/840
CMO.55/10

Committee on the Carcinogenic Action of Mineral Oils

Progress Report
by
H.N. Green and M.J. Radcliffe
Department of Experimental Pathology and Cancer Research
School of Medicine, Leeds.

Mouse Experiment.

Fractions used:-

$L_4S_2\frac{1}{2}$ = a

$L_4S_6\frac{1}{2}$ = b

L_4S_14 = c

0.01% D.M.B. = d($\frac{1}{10}$)

$L_4S_5\frac{1}{2}$ = e

0.05% D.M.B. = d($\frac{1}{2}$) = f

L_4SR = g

$L_4S_4\frac{1}{2}$ = h

$L_4S_7\frac{1}{2}$ = i

$L_4S_3\frac{1}{2}$ = j

$L_4S_8\frac{1}{2}$ = k

The experiment was begun on 7.6.55.

Tumours have been produced as follows:-

b ($L_4S_6\frac{1}{2}$) 3 tumours, at 9, 13 and 18 weeks.

c (L_4S_14) 2 tumours, at 13 and 14 weeks

d($\frac{1}{10}$) (0.01% D.M.B.) 1 tumour at 14 weeks

f (0.05% D.M.B.) 9 tumours, 1 at 11 weeks, 2 at 14 weeks, 2 at 16 weeks and 4 at 18 weeks

i ($L_4S_7\frac{1}{2}$) 3 tumours, 1 at 17 weeks and 2 at 18 weeks

k ($L_4S_8\frac{1}{2}$) 1 tumour at 18 weeks.

Survivors at 18 weeks are as follows:-

a 45 b 32 c 39 d 35 e 20 f 44

g 29 h 29 i 21 j 19 k 17

Rabbit Experiment

This was begun on 23.8.55. The beginning of the experiment was delayed owing to an epidemic of pneumonia amongst the rabbits.

Five rabbits have died since the experiment began.

So far no tumours have been produced.

(The dilutions of D.M.B. for rabbits are 0.2% and 0.05%).

INSTITUTE OF PETROLEUM RES-2-15

RESEARCH NO 2 COMMITTEE

Minutes of Meeting No.15 held at 26 Portland Place On Tuesday.20-9-55

ATTENDANCE

IN THE CHAIR:	F.Morton.
GUEST:	P.H.B. Trasler
MEMBERS:	T.S. Ault J.N. Haresnape R.B. Killingsworth W. Pohl H.W. Stevenson
APOLOGIES FOR ABSENCE:	E.J. Boorman J.W. Cook E.J. Dunstan A. McLean
SECRETARY:	E. Herbert

1. MINUTES OF MEETING NO.12

These were signed as correct, subject to the addition of "Shell Petroleum Co.," at the beginning of line 3 of the last paragraph of Minute 3 - I (Page 2)

2. MEMBERSHIP

The meeting accepted the resignation of Mr. W. Pohl with regret and desired to record its thanks to him for his valuable services. The nomination of Mr. H.W. Stevenson was approved by the Committee, who were glad to welcome him back as a Member.

3. WORK AT BIRMINGHAM UNIVERSITY

The Chairman reported on the progress of work at Birmingham University and drew attention to the paper "The Constitution of Petroleum Fractions; Structural Group Analysis of a Kuwait Heavy Gas Oil" which was presented at the recent World Petroleum Congress, and to various documents circulated by the MRC, in particular MRC 55/510 CAMO Minute 18 and CAMO 55/5

The Chairman distributed tables (dated September 20th 1955) of Analytical Data on Kuwait, Lagunillas and Oklahoma Crude Oils and mentioned that work in connection with Table 5, Sub-fractions from aromatic extracts, was now being carried out at Glasgow. The results indicated a very considerable potency concentrated in residues. There were small quantities of Kuwait Crude left over; it was proposed to blend fractions K4S2Aa/K4S5Ab and K4S6Aa/K4S8Ab and then redistil the blends for further test.

There would also be available some samples prepared from a Commercial Extract supplied by the Isle Grain Refinery. The Chairman mentioned that the Langunillas tests were a year behind owing to the withdrawal of the Chester Beatty Institute. This work was being carried on by Professor Green of Sheffield/Leeds University, but no medical school had been found to take an interest in the Oklahoma Crudes, which were therefore, being stored in their fractionated state.

Professor Morton added that he would prepare for publication in the IP journal a further paper in continuation of that presented at the World Petroleum Congress.

4. DIESEL GASES FUMES

The Chairman thanked Dr. Killingsworth for the material which he had provided for the report to the MRC and referred to a letter dated the 14th December 1954 from Mr. A. Fogg of MIRA in which, on behalf of the Diesel Engine Manufacturers, the IP were asked to draw attention of the major petroleum companies to the necessity to carry out investigations with the object of eliminating any exhaust smoke which might be attributable to fuel variations.

It was agreed that a general interest in the problem, which was separate from the medical aspect of smoke, was indicated but that it was a matter more for the Research Committee. Mr. Ault who promised to raise the subject at the meeting of MIRA which he was attending the next day was invited by Professor Morton to the next meeting of the Research Committee.

5. ANY OTHER BUSINESS

The Chairman intimated that he would shortly provide for circulation a copy of Mr. A.W.E. Poll's Thesis.

6. DATE OF NEXT MEETING

To be arranged by the Chairman.

CAR LIFE REPORT TO CONSUMERS

car exhausts and

By WILLIAM TERRELL

THERE IS A TICKING BOMB on the very doorstep of the American automobile industry and no one, including the scientists who discovered it, seems to know what to do about it.

The explosive discovery, which poses a greater potential threat to the motoring public, and to the American economy in general than any nuclear device, was brought to light last fall by Dr. Paul Kotin, one of the world's top cancer researchers. He told a group of distinguished colleagues that automobiles, trucks and buses are a primary cause of lung cancer!

Dr. Kotin, assistant professor of pathology at the University of Southern California Medical School in Los Angeles, stunned fellow scientists at the eighth annual lung cancer symposium of the Detroit Institute for Cancer Research with this flat, unqualified statement:

"Vehicular exhausts represent the most common, universal and probably greatest source of emitting known cancer-producing materials into the atmosphere in certain areas."

If Dr. Kotin and others are correct, this means that unless and until *something drastic is done*, the millions of cars, trucks and buses on the highways today and those yet to be produced along present engine design will continue to pour out enormous amounts of noxious gases daily, helping to swell the alarming lung-cancer death rate among city dwellers.

What is the automobile industry doing about this menace at present? Apparently all it can. The problem of automotive exhaust is not a new one—although until very recently it was regarded as merely a smelly, eye-smarting nuisance rather than a potential mass killer. Manufacturers, singly and as a group, for some time have been funneling money into research and field tests, trying to come up with a positive answer.

The road has been rough and the climb steep. In the first place, the scientists to whom the car manufacturers first turned were far from agreed on the role of auto exhausts in the rising lung-cancer incidence. The ground was virtually unbroken when the Automobile Manufacturers Association Vehicle Combustion Products Subcommittee pitched in to help Los Angeles rid itself of choking smog. New testing and evaluation techniques had to be developed and proved; new analytical methods had to be devised.

At the time, few among the top-drawer scientists exploring air pollution, and no one in the industry, even suspected what Dr. Kotin and others, equally eminent in the field, were to

Shocking charges have been made about the effect of auto exhaust fumes on America's health. For the first time, here is the complete truth about your car and lung cancer.

cancer

conclude: that exhaust fumes definitely *can* cause cancer.

However, when Dr. Kotin uncov-d the bomb, few people outside of .entific circles heard the news. Newspaper readers in New York found a four-paragraph Associated Press dispatch in the *Daily Mirror*, and *nothing* elsewhere. A check revealed that a national newspaper clipping service found *only one other newspaper in the country* that carried the dispatch at all: the *Los Angeles Times*.

Coincidence? Perhaps. It certainly wasn't because Dr. Kotin was vague.

Dr. Kotin told the Detroit symposium that mice used in tests have developed lung tumors after breathing compounds present in gasoline and diesel engine exhausts. Known cancer-producing chemicals have been found in exhaust products, he said.

Dr. E. Cuyler Hammond, chief of the American Cancer Society's statistical and research section, points out:

"The number of motor vehicles now registered in the United States is nearly three times as great as the base period (1924-26) and motor fuel consumption is more than five times as great. Although no exact measure is available, traffic congestion in cities and on highways near cities has probly risen to an even greater degree. ierefore, the increase in fumes from this source, particularly near cities and highways near cities is really tremendous."

Tremendous indeed! All this, coupled with the dust from bituminous roads, which have increased six-fold in the same period, and others surfaced with asphalt and oil products, which have increased many times more, presents a formidable picture.

RESEARCH into air pollution generally was dramatized and probably stimulated to its present degree by a series of tragic episodes in Belgium, Donora, Pa., Mexico and London, between 1930 and 1952. Since then an army of researchers has been studying air pollution generally and, more recently, by the combustion of fuels, with emphasis on hydrocarbons, the known cancer producers.

Their studies have revealed that significant, even alarming, amounts of carcinogenic (cancer-producing) substances are poured into the air we must breathe by the machines of our industrial age—especially automotive machines.

Writing in *The Scientific Monthly*, Dr. Lauren B. Hitchcock, president and managing director of the Air Pollution Foundation in Los Angeles and one of the giants in the field, observed in part:

"As our cities expand, more public and private transportation is needed in the form of motor vehicles and increased power requirements. This is the age of mechanization, and virtually all machines require power produced by a combustion process. Our present combustion processes are all very imperfect and contribute by far the major part of man-made pollution. Improvement of combustion processes should be the first major goal of science and technology.

"Vehicle combustion products are a major source of air pollution. Total motor-fuel consumption in the United States today is about 150 million tons per year; although the actual amount of automobiles never has been accurately determined, it is calculated that one gallon of gasoline produces 1,000 feet of exhaust gas on the dry basis."

That residual hydrocarbons are responsible for much of the increase in urban lung cancer and for much of the difference between the urban and rural incidence of the disease is accepted now by virtually every recognized authority, many of whom have been saying so in medical and other scientific journals for some time. To just what extent these fumes are responsible has not and may never be determined. But the experts have a number of good clues.

(Continued on page 63)

CANCER

(Continued from page 17)

AS THE American Cancer Society's Dr. Cuyler Hammond shows, the death rates from cancer in all parts of the body have been increasing steadily for a great many years. However, cancer death rates rise with age, and most of the increase is attributable to the aging of our population. With one notable exception, Dr. Hammond says, death rates by ages for cancer in various locations have not changed greatly during the past several decades. The exception is lung cancer, for which the age-standardized death rate among males has risen from about 0.7 per 100,000 in 1914 to 3.6 in 1930 to 19.5 in 1950. And among females it has risen from about 0.6 per 100,000 in 1914 to 4.3 in 1950. That means that about 17,400 males and 3,500 females died of lung cancer in 1952, the most recent year for which estimates are available.

To get at some of the questions arising from these statistics, Dr. Hammond has adopted as a working hypothesis (1) that human beings vary in their susceptibility to lung cancer; (2) that some, if not most, cases of lung cancers are produced by a substance or combination of substances inhaled into the lungs, and (3) that the lungs must be exposed to the substance or substances for varying periods of time, up to 30 or more years, depending upon the cancer-producing potency and concentration of the substance, as well as the susceptibility of the individual.

"Fumes from burning petroleum do contain measurable quantities of known carcinogenic agents, and human beings do inhale those fumes," he says, as strongly as a scientist of his stature is likely to permit himself. *"It has been shown that an idling automobile engine gives off about one milligram of benzpyrene per minute. No small quantity of this known carcinogen must be present at nose level in the air of a heavily congested city street."*

In sum, it may be said that the potency of hydrocarbon waste in the air is known and accepted. And while its exact place in pollution of the air we breathe has not been fully established, our knowledge is too meager to permit complacency.

Who, then, besides Dr. Kotin are engaged in this vital area of research? There are many, among whom Dr. Kotin seems merely to have been the most vocal. These men, working away in their laboratories, receive 90 per cent of their funds from the four major agencies sponsoring cancer research in this country: The National Cancer Institute, the American Cancer Society, the Damon Runyon Memorial Fund and the Atomic Energy Commission. Private funds, such as those of the Tobacco Industry Research Council and the Automobile Manufacturers Association, to name but two, make up the other 10 per cent. All of these funds are given without strings for basic research in a given area and the donors have no control over the direction which such research might take. Thus, it is possible that Dr. Kotin, working with a grant from Chrysler, among others, might come up with data relating car exhaust to lung cancer.

Of course, each investigator, being human, is influenced to some degree by the direction of his own research. Thus, some may stress or discount the importance of this agent or that in producing human lung cancer. Many reputable scientists, for instance, feel that Dr. Kotin is too brash and should have gathered more evidence before he spoke out.

Then, of course, there is a widely held belief, espoused by Drs. Cuyler Hammond and Daniel Horn, of the American Cancer Society, that cigarets account for at least 70 per cent of the difference in the urban and rural lung cancer death rates.

Then again, a spokesman for the Damon Runyon Fund, admitting the contribution of cigarets, car exhaust and other factors to the general picture, offered the following excerpt from a Walter Winchell radio broadcast as a statement of his organization's stand at the moment:

"The real threat in lung cancer . . . is the atomic fallout. By 1957 *there will be twenty-five atomic reactors operating in the United States and as many abroad . . . fifty in all. The fallouts from these reactors, plus atomic dust from test explosions, constitute the real hazard—to everything you eat, smell or breathe. The points of concentration of this radioactive material are the lung and thyroid glands. The Runyon Cancer Fund, incidentally, has invested more than a half million dollars of your donations in air pollution research studies."*

The auto industry keeps hitting the problem hard in its own quiet, effective way. Both the American Petroleum Institute and the Automobile Manufacturers Association are sponsors of a Coordinating Research Council. To attack the present problem, the CRC has established a group to study exhaust gases, and under it four special panels to develop instruments and procedures needed for accurate sampling and analysis of exhaust gases; to find out how fuels, engine designs and operating conditions affect exhaust; and to make actual tests on cars in the field.

Meanwhile, the AMA's Vehicle Combustion Products subcommittee has also established four working panels. The Induction System panel is concentrating on devices to improve operation at the fuel intake end of the engine. The Exhaust System panel is concerned with means of cleaning up the exhaust after it leaves the engine but before it reaches the air. The Traffic Survey panel is studying actual driving conditions and driver habits, and the New Devices panel is routing all devices they regard as promising from the outside to the proper industry group. The AMA board of directors has ordered a patents cross-licensing agreement and it has been joined by all participating companies.

WHERE DOES the automotive industry stand now in its "million-dollar search" to eliminate the menace of car exhaust? John M. Campbell, chairman of the AMA's Vehicle Combustion Products Subcommittee and administrative director of General Motors' research laboratories, said after Dr. Kotin's stunning announcement:

"I know that many of you (attending the Southern California Conference on Elimination of Air Pollution in Los Angeles) *have been waiting to hear what my industry has to report, since the scientific consensus is that, as of today, automotive exhaust gases contribute the largest share of chemical materials to the reaction that gives you 'smog.'*

"I am not going to quibble over the exact proportions of the automotive contribution. That will be established on a much firmer footing in the near future. Suffice it to say that I think, and so does my industry, that it has been clearly enough established that our contribution is significant, and so must be reduced as much as possible, as fast as possible.

"We are promising no miracles. Our first goal is an absolute minimum reduction of 50 *per cent in the emission of unburned hydrocarbons from cars and trucks. I believe that we will actually give you considerably greater reduction with our first devices, and we'll keep on working for further improvement. But let's suppose we come up with* 100 *per cent reduction. What then?*

"When automotive devices are available, it will still be up to local citizens in the final analysis to see that they are used to the best effect. I can promise you that these devices will be as

(Continued on page 71)

CANCER

(Continued from page 63)

efficient and inexpensive as we know how to make them, but their proper installation, maintenance and use will be a problem of local regulation. It's going to be costly, not only in original investment, but in keeping inspection and enforcement at a high peak of efficiency. You may also have to sacrifice something in the performance of your vehicles."

There are at present several approaches to the problem. Since the noxious fumes result from incomplete burning of the fuel, especially at idle and deceleration, the trick has been to eliminate excess fuel either before or after it leaves the cylinders.

This can be accomplished by an afterburner, which involves the additional hazard of an open spark or flame; by a so-called catalytic muffler, which depends on oxidation of the exhaust gas as it passes over a chemical; or by devices which limit manifold vacuum or cut off the flow of fuel to the cylinders in the deceleration cycle. There are several companies experimenting with all of these devices, but experts question whether they are effective and for how long.

Top industry spokesmen fear that a panicky public may demand legislation which could force motorists to invest a sizable amount of money—perhaps $50 per car—for something that may not even be a palliative.

Apropos of this, James C. Zeder, vice president and director of engineering and research of the Chrysler Corporation, told a symposium on air pollution not long ago:

"How good are these devices? Frankly, I don't know. One device, representative of those under industry study, is on the Chrysler Corporation car which I have been using. It has given promise of reducing hydrocarbons in exhaust fumes by as much as 90 per cent during deceleration. It has performed reasonably well so far, but that doesn't satisfy us.

"Before we in the automobile industry consider a device promising it has to operate for hundreds of thousands of miles in good weather and bad, in broiling heat and bitter cold. It must be shaken over rough roads and, in the case of carburetion, must gasp for air on mountain peaks. Bitter experience has taught us that this testing cannot be by-passed. Even with every test which we can devise, some drivers will manage to get into situations we did not foresee."

The best estimate on the time this search for an effective remedy will take is several years—perhaps five. Again, all you can do is wait. If it does turn out that devices costing around $50 are needed, it will present a very attractive one-shot market representing an expenditure of some $100 million by the public.

But, as Mr. Zeder, said: *"It amazes me to see how much headway this undertaking has picked up. After a little more than a year on the job, our people do know which way they are going even though all the answers aren't uncovered. But we have reached a point where we can compare devices, exchange ideas and start the serious test work on the best of them."*

That, then, is the picture. Not only the independent research scientists, but combustion engineers of the several AMA members are working in their company laboratories. They meet regularly for free exchange of findings and ideas.

Most of all, however, the problem needs airing. By pressure, design or coincidence—or a combination of each—the press has almost entirely ignored the possible relationship between automotive exhaust and the rising incidence of lung cancer.

What can the public do until proven devices arrive to alleviate the menace?

Laws might be passed banning cars from the highways. Ridiculous? Perhaps. But remember that in wartime automotive travel was cut to a necessary minimum and an aroused public could bring about even stricter enforcement. However, it is doubtful that such a drastic step will need to be taken.

Perhaps new and revolutionary engine design could eliminate the problem entirely in new cars. But that would take more time and we would still have the question of what to do with the cars, trucks and buses already on the road.

SOMEWHERE there lies an answer. But whether it rests in stepped up medical research, in revolutionary new engines, in preventative devices or in curtailment of car use, one fact above all is certain. The answer does not lie in secrecy or suppression.

All the facts must be published for every American to read and understand. It is only in this way that the answer will be found—through public awareness and determination to do something about it.

Exhaust fumes must be reduced "as much as possible as fast as possible," stated GM's John M. Campbell.

Americans can only hope it won't also be too little and too late. ●