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SHELL OIL COMPANY, INCORPORATED

WOOD RIVER RESEARCH LABORATORIES

REPORT NO. M-1247

JULY 2, 1945

SUBJECT: CARCINOGENIC HYDROCARBONS AND RELATED COMPOUNDS

A LITERATURE REVIEW

AUTHOR: H. H. ZUIDEMA

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A LITERATURE SURVEY

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A LITERATURE REVIEW

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Industrial cancer was first recognized in England in the latter part of the eighteenth century, when it was established that chimney sweeps were particularly liable to cancer of the scrotum.[10] This was caused by soot. Progress in this field of study was very slow at first, and it was not until 1915 that two Japanese investigators announced the first case of carcinoma in an experimental animal. They produced first papillomas and then true cancer of the epidermis on the ears of rabbits by painting with tar over long periods of time.[35] During the thirty years that have elapsed since that discovery, a great deal of work has been done with various coal tar and petroleum fractions and pure compounds either occurring in these fractions or prepared synthetically. Numerous species of test animals, including mice, rats, fowl, rabbits, and dogs have been used, and many methods of application, including oral administration, intramuscular, intravenous, and subcutaneous injection, and painting on the skin. The method that appears to be the most widely used at present consists of painting a solution on the skin of a special inbred strain of mice. Mice are preferred over animals having longer life-spans since they respond more rapidly. The special strains are used to increase the precision of the test. Painting is preferred to other methods of application because there is less likelihood of interference by simultaneous spontaneous carcinomata. The carcinogenicity of a given compound is influenced by many factors including the genetic consitution of the animal species and strain, its age and sex, the diet, the physical condition of the animal, the purity of the compound, the dose, the physical state of the compound, the solvent used, and the route or site of application.[25]

While carcinogenic properties are generally associated with certain polynuclear aromatics and their derivatives, there are many substances entirely unrelated to these compounds which have been reported as having similar cancer-producing ability. Among these may be mentioned asbestos[34,37], inorganic compounds of arsenic and of zinc[25], aqueous potassium hydroxide and aqueous hydrochloric acid[25], ethyl alcohol[25], glucose[25], fructose[25], and a number of nitrogen compounds, most of which contain one or more benzene rings[25]. Radioactive elements and compounds are not included in this discussion since the mechanism of their producing cancer is probably quite different, i.e., physical rather than chemical. Materials which have been reported

as carcinogenic and whose carcinogenicity is probably due to the presence of polynuclear aromatics include coal tar and pitch[26,27] blue shale oil[5], mineral oils and asphalt[43], tobacco tar[39], tars obtained in the destructive distillation of tea[42] and coffee[40], diesel fuel[52], distillates from Borneo crude petroleum[54], combustion gases from fuel oil[41], the SO_2 extract from a spindle oil produced from a paraffinic crude petroleum[54], the products obtained by heating acetylene, isoprene, yeast, a non-carcinogenic petroleum fraction, or human skin to 700 - 900°C[30], and the products obtained by treating acetylene, xylene, naphthalene, or tetrahydronaphthalene with aluminum chloride[31]. The carcinogenicity of tars produced by heating various substances tends to increase with increasing temperature.[30,45] It is probable that the carcinogenic hydrocarbons present in certain coal tar and petroleum fractions were to a large extent formed during the process steps and were not present in the coal or crude petroleum from which they were derived. However, the carcinogenicity of a given fraction depends upon the source as well as the method of processing. According to the Manchester Committee on Cancer[49], the following order of increasing carcinogenicity prevails: Russian, Pennsylvania, Texas, Mid-Continent, Mexican, California, Persia, Romanian, Borneo, Venezuela, and shale. This corresponds roughly to the order of increasing aromaticity.

A large number of compounds have been tested for carcinogenicity. Hartwell has published a survey[25] which includes 696 compounds tested. Of these, 146 were carcinogenic, and 23 additional ones produced papillomas but no true cancers. While some of these compounds have been tested under only one or two sets of conditions, others have been studied very extensively. The three compounds that have received the most detailed study are the three derivatives of 1,2-benzanthracene: 1,2,5,6-dibenzanthacene, 3,4-benzpyrene, and 20-methylcholanthrene. All three are potent carcinogens. It has been estimated that they have been investigated in 60 different laboratories.[20]

A list of most of the known carcinogenic compounds is given in Table 1, pages 5-10. Structures, complete with numbering systems, are included, since lack of uniformity among various investigators in this field has led to some confusion. There is fortunately less deviation in the current papers than in the case of those written ten to fifteen years ago. The numbering used in this report corresponds to that used by Hartwell[25]. It should be understood that the carcinogenicity of the compounds shown in Table 1 varies considerably in degree and that the results have been verified by several laboratories in some cases while in others the results of only one or two experiments are available. The reader is referred to Hartwell for more detailed information and for reference to the original experiments. It will be observed that most of the compounds are either hydrocarbons or their derivatives containing at least three benzene rings or nitrogen compounds containing at least two benzene rings. More specifically, the first of these classes consists, with only three exceptions, of derivatives

of phenanthrene. The exceptions are tetraphenylmethane, triphenylbenzene, and triphenylethylene. In Table 1 the hydrocarbons are subclassified further as derivatives of 1,2-benzanthracene, 3,4-benzpyrene, cholanthrene, and other derivatives of phenanthrene. Examination of the structures shows that all of these are derivatives of phenanthrene.

While the work that has been done on the production of cancer by exposure to various compounds has made it possible to draw certain conclusions regarding the effect of chemical structure, it is not as yet possible to predict with any degree of certainty the carcinogenicity of a given compound from its structure. A phenanthrene derivative may or may not, for example, be carcinogenic depending upon such factors as the length of an alkyl side chain, the position of a benzene ring, or the position of an alkyl group. However, a paraffinic or naphthenic hydrocarbon or one containing only one or two benzene rings may with a reasonable degree of confidence be assumed to be non-carcinogenic.

The amount of compound required to produce an experimental cancer on a test animal is surprisingly small. Doses of 1,2,5,6-dibenzanthracene and 3,4-benzpyrene as small as 2.5 and 4 micrograms, respectively, give positive results when applied to mice.[16,23] Discontinuous application, e.g., once a week, of a given total quantity of material is more effective than continuous exposure.[15] A single application of 20-methylcholanthrene in 0.6% benzene solution is capable of producing cancer on the skin of mice.[45] When different carcinogenic hydrocarbons, e.g., methylcholanthrene, benzpyrene, and dibenzanthracene, are applied successively the effect is additive[35]. The investigators who made this observation offer the hypothesis that carcinogenisis is essentially an accumulation of abnormal protein within the cell.

Since so many compounds have been tested for carcinogenicity it is only natural that several attempts have been made to correlate this property with other properties, either physical or chemical. Such a correlation would be extremely useful in that the determination of the physical or chemical property would be much simpler than the rather long and tedious process of exposing experimental animals to the substance in question. Fluorescence spectra have received more study in this regard than any other property.[5,7,28,32] The author of a recent paper made the statement that all known carcinogenic chemicals are fluorescent.[43] However, it is obvious from a glance at Table 1 or Hartwell's tabulation that this is too broad a claim. However, many investigators have used fluorescence spectra to good advantage in this field, and there appears to be a definite correlation with carcinogenicity, at least with certain types of compounds. The correlation may be due in part to the fact that fluorescence spectra have been used as a guide in selecting fractions from coal tar for physiological tests; it is conceivable that other carcinogenic compounds, which are not fluorescent, exist or could be synthesized.

A rough parallelism between the carcinogenicity of polynuclear aromatics and the diazo coupling reaction has been observed.[21,22] Attempts have also been made to correlate refractive index, or more specifically, specific refraction, with the carcinogenicity of oils.

The Manchester Committee on Cancer[49] recommended that spindle oils of various ranges of specific gravity have specific refraction values below certain limits to assure the absence of carcinogenic properties. However, it is obvious that there can be no general correlation between a physical property of this nature and carcinogenicity, for slight changes in structure, such as the position of a methyl group, which would have little effect upon optical properties, affect carcinogenic properties profoundly; furthermore the presence of a large concentration of a non-carcinogenic aromatic would raise the specific refraction of a mixture much more than would the presence of a small amount of a potent carcinogen.

The probability of obtaining a general correlation between carcinogenicity and some more easily determined property would be greatly enhanced if there were a clearer understanding of the mechanism of the action of carcinogenic compounds. It is, of course, very difficult to obtain such an understanding, for so little is known about cancer itself.

Whether or not carcinogenisis by hydrocarbons and related compounds is in any way connected with spontaneous cancer is a question that has received much conjecture. That such a relationship does exist is suggested by the fact that certain derivatives of estradiol (see Table 1) which is closely related to the sex hormone estrone, are carcinogenic. Spontaneous cancer quite often occurs in the reproductive organs. Furthermore, the very potent carcinogen, 20-methylcholanthrene, can be produced by the degradation of desoxycholic acid, cholic acid, or cholesterol, the first two of which are normal constituents of human bile and the last of which is present in all tissues of the human body.[22] These degradation reactions were, however, conducted under drastic conditions which are in no manner related to those prevailing physiologically, and there is no evidence that 20-methylcholanthrene is formed in the body through the degradation of bile acids or cholesterol. The possible connection between cancer produced spontaneously and carcinogenisis by methylcholanthrene or related compounds therefore remains a matter of conjecture, at least for the present.

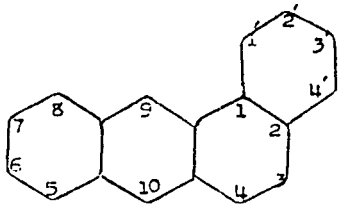
There has, for obvious reasons, been little attempt to induce cancer in human beings through exposure to the various compounds that are carcinogenic to mice. There is, therefore, no direct correlation between the susceptibility of man and the test animals. There is, of course, an indirect correlation of occupational cancer largely through exposure to coal tar and dye intermediates caused by materials which are carcinogenic to mice. However, many of the compounds shown in Table 1 do not occur in any products known to have caused occupational cancers, and it is conceivable that some compounds harmful to mice are innocous to man. Until that can be proved, the only safe policy is to regard all compounds which are harmful to mice as dangerous and to avoid exposure by humans.

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TABLE 1

CARCINOGENIC COMPOUNDS

All compounds listed by Hartwell[25] unless otherwise indicated.

1. Derivatives of  1,2-benzanthracene

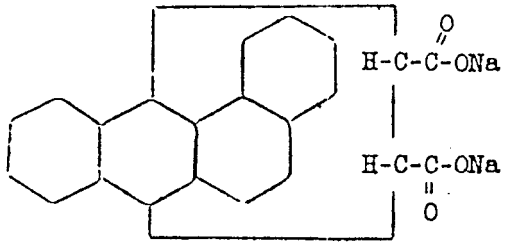
The following derivatives of 1,2-benzanthracene:

3-methyl
5-methyl
6-methyl
9-methyl
5-ethyl
10-ethyl
5-n-propyl
5-n-butyl[2]
5-n-amyl[2]
5-n-hexyl[2]
6-i-propyl
3-hydroxy
10-hydroxy
10-aldehyde, $-\overset{H}{\underset{|}{C}}=O$
10-methyleneacetoxy, $-\overset{H}{\underset{H}{\overset{|}{C}}}-O-\overset{O}{\overset{\|}{C}}-CH_3$
10-methylenecarbomethoxy, $-\overset{H}{\underset{H}{\overset{|}{C}}}-\overset{O}{\overset{\|}{C}}-O-CH_3$
10-cyanomethyl, $-\overset{H}{\underset{H}{\overset{|}{C}}}-CN$
3-methoxy
10-methoxy
4,9-dimethyl
4,10-dimethyl
5,6-dimethyl
5,9-dimethyl
5,10-dimethyl
6,7-dimethyl
9,10-dimethyl
6,7-dimethyl
9,10-dimethyl
5-chloro, 10-methyl
7-chloro, 10-methyl
5-cyano, 10-methyl
7-cyano, 10-methyl
1,2,7,8-dibenzanthracene[31]
1,2,5,6-dibenzanthracene

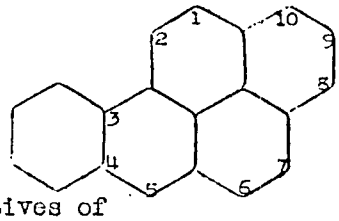
The following derivatives of 1,2,5,6-dibenzanthracene:

9-methoxy
2′-methyl
3′-methyl
4-methyl
9-methyl
1′,9-methylene 
4,10-dimethylene, 
3,4′-dimethylene (phenanthra-acenaphthene)
8,9-dimethylene

5,6-cyclopenteno 
6,7-cyclopenteno
1′,2′,3′,4′-tetrahydro
Na salt of 9,10-endo alpha,beta succinic acid:



2. Derivatives of 3,4-benzpyrene



3,4-benzpyrene

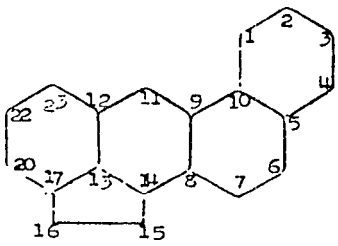
The following derivatives of 3,4-benzpyrene:

5-aldehyde
4′-methyl
5-methyl
1′,2′-dihydro, 4′-methyl

1′,2′,3′,4′-tetrahydro
10-acetyl

3,4,8,9-dibenzpyrene
5,10-dihydro-3,4,8,9-dibenzpyrene
7-methyl,1,2,3,4-dibenzpyrene

3. Derivatives of Cholanthracene



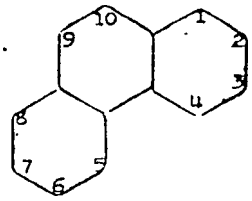
Cholanthrene

The following derivatives of cholanthrene:

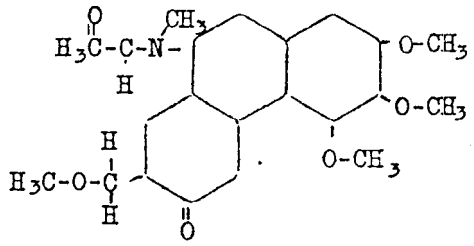
20-methyl
20-ethyl
20-isopropyl
20-tert-butyl[44]

15,20-dimethyl
16,20-dimethyl
15-hydroxy, 20-methyl
15-keto, 20-methyl

4. Other Derivatives of Phenanthrene

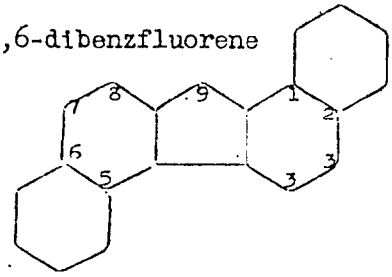


Colchicine



3,4-benzphenanthrene

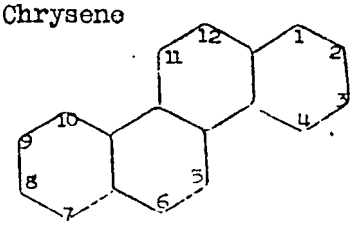
1,2,5,6-dibenzfluorene



The following derivatives of 3,4-benzphenanthrene

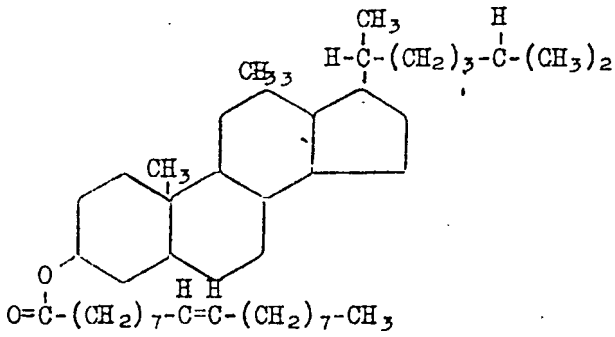
1-methyl[2]
2-methyl[2]
2-ethyl[2]
2-isopropyl[2]
7-methyl[2]
8-methyl[2]
2,9-diethyl
2-methyl, 1,2,3,4-dibenzphenanthene

Chrysene

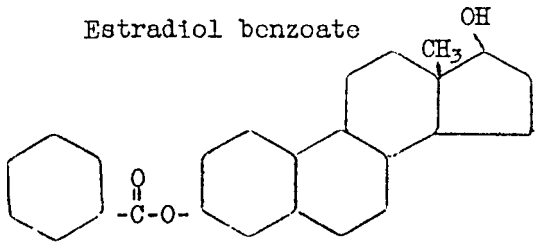


1,2-dimethyl chrysene[2]
5-methyl chrysene[17]
4,5-methylene chrysene[17]
5,6-dimethyl chrysene[17]

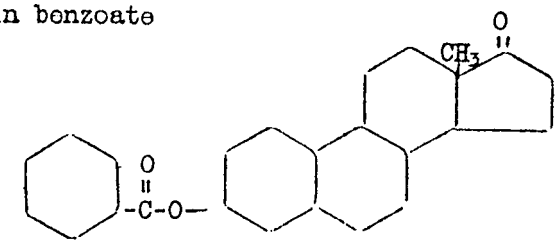
Cholesterol oleate



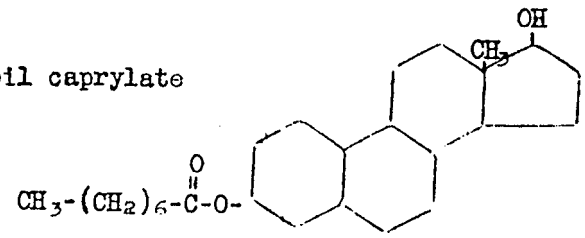
Estradiol benzoate



Equilenin benzoate

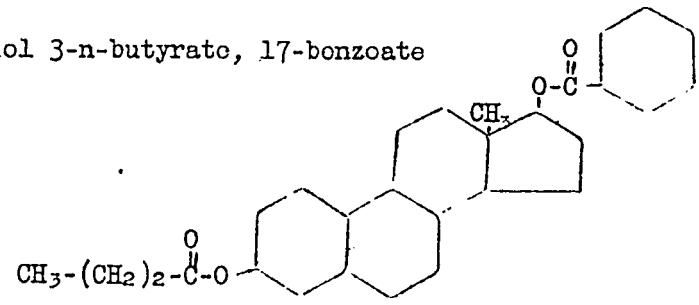


Estradoil caprylate



1,2-cyclopentene phenanthrene[2]

Estradiol 3-n-butyrate, 17-benzoate

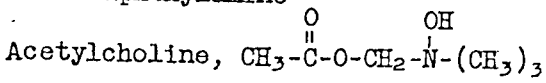


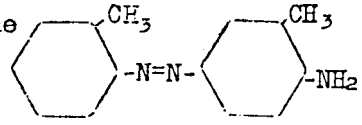
5. Other Aromatic Compounds

Tetraphenylmethane
1,3,5-triphenylbenzene
Triphenylethylene[33]

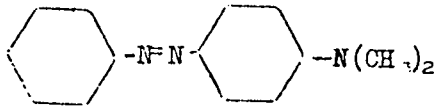
6. Organic Compounds Containing Nitrogen

2-amino, 1-naphthol
Alpha naphthylamine[13]
Beta-naphthylamine

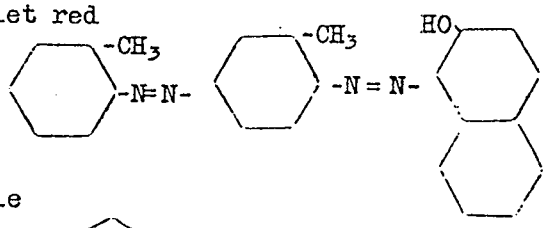
Acetylcholine, 

o-amino azotoluene 

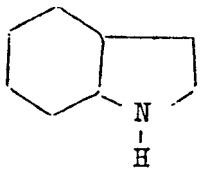
p-dimethyl aminoazobenzene (butter yellow)



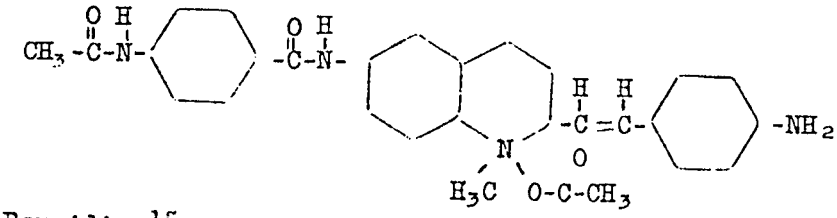
Scarlet red



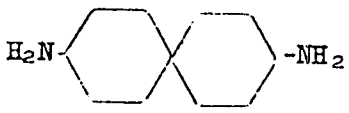
Indole



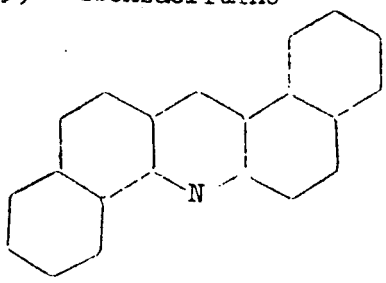
Syyryl 430



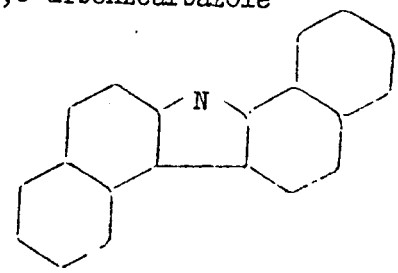
Benzidine[13]



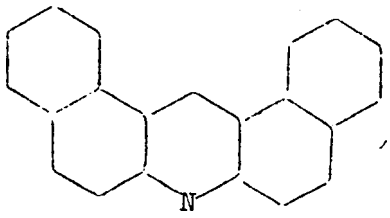
1,2,5,6-dibenzacridine



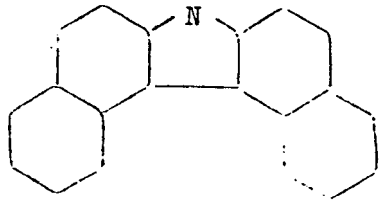
1,2,5,6-dibenzcarbazole



1,2,7,8-dibenzacridine



3,4,5,6-dibenzcarbazole



7. Miscellaneous

Arsenic trioxide
Potassium arsenite
Aqueous hydrochloric acid
Aqueous potassium hydroxide
Zinc chloride
Zinc sulfate
Ethyl alcohol
Fructose
Glucose
Galactose

BIBLIOGRAPHY

1. Auld, S. J. M., J. Inst. Pet. Tech., 24, 577-83 (1938).

2. Badger, G.M., Cook, J.W., Hewett, C.L., Kennaway, E.L., Kennaway, N. M., Martin, R.H., and Robinson, A.M., Proc. Roy. Soc., B129, 439-67.(1940)

3. Badger, G.M., Cook, J.W., Hewett, C.L., Kennaway, E.L., Kennaway, N.M., and Martin, R.H., Proc. Roy. Soc., B131, 170-82 (1942).

4. Barry, G., Cook, J.W., Haslewood, G.A.D., Hewett, C.L., Hieger, I., and Kennaway, E.L., ibid, B-117, 318-51 (1935).

5. Berenblum, I., and Schoental, R., Brit. J. Exp. Path., 24, 232-9 (1943).

6. Bottomley, A.C., and Twort, C.C., Am. J. Cancer, 21, 781-8 (1934).

7. Bruce, W.F., and Todd, F., J. Am. Chem. Soc., 61, 157-61 (1939)

8. Campbell, J.A., Brit. J. Exp. Path., 15, 287-94 (1934).

9. Campbell, J.A., ibid, 20, 122-32 (1939).

10. Cook, J.W., Nature, 145, 335-8 (1940).

11. Cook, J.W., Haslewood, G.A.D., Hewett, C.L., Hieger, I., Kennaway, E.L., and Mayneord, W.V., Am. J. Cancer, 29, 219-59 (1937).

12. Cook, J.W., and Kennaway, E.L., ibid, 33, 50-97 (1938).

13. Cook, J.W., and Kennaway, E.L., ibid, 39, 381-428, 521-82 (1940).

14. Cook, J.W., Hieger, I., Kennaway, E.L., and Mayneord, W.V., Proc. Roy. Soc., B111, 455-84 (1932).

15. Cramer, W., and Stowell, R.E.,Cancer Research, 3, 668-81. (1943)

16. Dobrovolskaya-Zavadskaya, N., Compt. rend. soc. biol., 129, 1055-7 (1938).

17. Dunlap, C.E., and Warren, S., Cancer Research, 3, 606-7 (1943).

18. Evans, E.E., J. Urol., 38, 212-15 (1937).

19. Fieser, L.F., "Chemistry of Phenanthrene", Reinhold Publishing Company, N.Y., (1937).

Bibliography (Continued)

20. Fieser, L.F., Am. J. Cancer, 34, 37-124 (1938).

21. Fieser, L.F., and Campbell, W.P., J. Am. Chem. Soc., 60, 1142-5 (1938).

22. Fieser, L.F., and Fieser, M., "Organic Chemistry", pages 814-26, Heath and Co., Boston, Mass., 1944.

23. Gottschalk, R.G., Proc. Soc. Exp. Biol. Med., 50, 369-73 (1942).

24. Haddow, A., and Robinson, A.M., Proc. Roy. Soc., B127, 277-87 (1939).

25. Hartwell, J.L., U.S. Public Health Service, Nat. Inst. Health, Nat. Cancer Inst., 1941, "Survey of Compounds which Have Been Tested for Carcinogenic Activity", 371 pp.

26. Heller, I., J. Ind. Hyg., 12, 169-97 (1930).

27. Henry, S.A., Kennaway, N.M., and Kennaway, E.L., J. Hyg., 31, 125-37 (1931).

28. Hieger, I., Biochem. J., 24, 505-11 (1930).

29. Hueper, W.C., J. Ind. Hyg., 16, 255-79 (1934).

30. Kennaway, E.L., Brit. Med. J., 1925, II 1-4.

31. Kennaway, E.L., Biochem. J., 24, 497-504 (1930).

32. Kennaway, E.L., and Hieger, I., Brit. Med. J., 1930, No. 3622, 1044-6.

33. Lavik, P.S., Moore, P.R., Rusch, H.P., and Baumann, C.A., Cancer Research, 2, 189-92 (1942).

34. Linzbach, A.J., and Wedler, H.W., Arch. Path. Anat. (Virchow's), 307, 387-409 (1941).

35. Loeb, L., Alexander's "Colloid Chemistry", Vol. V, 995-1050 (1944), Reinhold Publishing Co., N.Y.

36. Morton, A.A., Clapp, D.B., and Brand, C.F., Science, 82, 134 (1935).

37. Nordmann, M., Z. Krebsforsch., 47, 288-302 (1938).

Bibliography (Concluded)

38. Robson, J.M., and Bonser, G.M., Nature, 142, 836 (1938).

39. Roffo, A.H., Prensa Med. Argentina, 26, 721-38 (1939).

40. Roffo, A.H., Bol. Inst. Med. Exp. Estud. Cancer, 15, 741-56 (1939).

41. Roffo, A.H., ibid, 16, No. 52, 1-6 (1939).

42. Roffo, A.H., ibid, 17, 661-98 (1940).

43. Roffo, A.H., and Roffo, A.E., Jr., ibid, 20, 143-87 (1943).

44. Shear, M.J., Leiter, J., and Perrault, A., J. Nat. Cancer Inst., 2, 99-113 (1941).

45. Simpson, W.L., and Cramer, W., Cancer Research, 3, 604-5 (1943).

46. Stallybrass, C.O., J. State Med., 34, 249-68 (1926).

47. Stowell, R.E., and Cramer, W., Cancer Research, 2, 193-7 (1942).

48. Twort, C.C., and Fulton, J.D., J. Path. Bact., 33, 119-43 (1930).

49. Twort, C.C., and Lyth, B., J. Hyg., 33, 464-73 (1933).

50. Twort, C.C., and Twort, J.M., J. Ind. Hyg., 13, 204-26 (1931).

51. Twort, C.C., and Twort, J.M., J. Hyg., 29, 373-9 (1930).

52. Twort, C.C., and Twort, J.M., ibid, 35, 130-49 (1935).

53. Twort, C.C., and Twort, J.M., Lancet, 1935, II, 1226-8.

54. Twort, J.M., and Twort, C.C., J. Hyg., 39, 161-9 (1939).

55. Woodhouse, D.L., J. Inst. Pet. Tech., 20, 1057-63 (1934).

For those wishing to acquire a more extensive background in this field, a review by Fieser[20] is recommended as a good starting point, followed by the original papers by Cook and co-workers. For a detailed tabulation of carcinogenic compounds Hartwell's book[25] should be consulted.