COMMENTS

In making the above preparations it is not necessary to avoid agitation. The formulas may be varied slightly as long as the p_H is maintained in the neighborhood of 4.5 to 5.5, and as long as 20% or more of glycerol is present. An alcoholic concentration above 15% should be avoided. For best results, the method of preparation should be carried out as directed above. If filtration by suction is not available, filtration by gravity may be employed, being certain that the filter paper is washed thoroughly with distilled water. Finally, the preparations should be assayed for peptic activity before placing in permanent flasks.

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Carcinogenics and Medicine*

By Seward E. Owen†

This report deals with a consideration of the carcinogenic chemicals, their sources, biological activity, chemistry and methods of detection as they relate to medicine.

Certain tars were first shown to be capable of producing cancer in experimental animals by Yamagiwa and Ichikawa (1) in 1913. Since that time much progress has been made in the clarification of the chemical formulas of substances capable of inducing malignant changes in the tissues of experimental animals. Important contributions are those of Bloch and Dreifuss (2) who showed that carcinogenic material in tar was contained in the nitrogen-free, neutral, high-boiling fraction. That the active substances were hydrocarbons was indicated by the work of Kennaway (3). Mayneord (4) first applied the fluorescent spectrum method to the problem. Heiger (5) later noted that many carcinogenics displayed similar fluorescence spectra. The absorption spectrum of 1:2:5:6 dibenzanthracene was first studied by Clar (6) and later by Chalmers (7). These early spectrum studies led the English scientists to try many compounds with similar spectra for possible carcinogenic effects on animals, with the result that 1:2:5:6 dibenzanthracene was found to be a potent cancer-causing agent when applied in solution to the skin of animals. By this technique cancers of the squamous variety were induced. Later Burrows, *et al.* (8), noted that the same agent in contact with connective tissue produced tumors of this tissue. Cook, *et al.* (9), synthesized a large number of similar compounds which were tested biologically. Among these were methylcholanthrene and 1:2 benzpyrene, both highly carcinogenic.

The most important carcinogenic chemicals that may exist in coal tar are 1:2 benzpyrene, 1:2:5:6 dibenzanthracene and possibly methyl cholanthrene. These are now made synthetically for experimental use and may be obtained from the standard chemical houses. Reviews from the chemical standpoint of carcinogenics have been presented by Cook and Kennaway (10) and by Fieser (11). These are rather exhaustive and complete. Many derivatives of the above carcinogens as well as some newer compounds are mentioned in the above papers. Other reviews consider the carcinogenics, sex hormones and sterols, all of which have the phenanthrene nucleus Owen (12) and Dodds (13). In this connection it is of interest to point out that some synthetic carcinogenics are estrogenic and that rather potent estrogenics may be derived from certain closely related, chemically, carcinogenic agents.

The test methods to demonstrate carcinogenic activity are those adopted by the English workers which consist of applying the hydrocarbons at 0.3% in benzene solution to the interscapular region of mice

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twice weekly, the applications usually being continued until tumors are noted or for a period of months. The technique utilized in leading American laboratories is that of Shear (14) who injects 5 to 10 milligrams as a solid moistened with a little glycerol. The injections are usually made subcutaneously into mice. A single injection is usually sufficient. The carcinogenic hydrocarbons are considered to be relatively insoluble in water or in aqueous salt solutions and most of them are but sparingly soluble in organic solvents as benzene, alcohol or lipids. As little as 0.4 gamma of 1:2:5:6 dibenzanthracene has caused the appearance of cancer. The use of the higher dosages as 5 to 10 mg. minimizes any variations connected with the dosage factor in analyzing a group of substances for carcinogenicity. Unfortunately, lard and the liquid and filtrable part of lard at 37° C. have been used as a solvent. This, however, is of a variable composition which may undergo changes on heating or on storage. Nearly all of our mice of the C3H strain have developed tumors following the injection of 0.25 mg. of the 1:2:5:6 dibenzanthracene (Owen (15)). Instances of varying susceptibility to the carcinogenics by various strains of mice are noted by Fieser (11). Average induction time of cancer ranges from 13 to 30 weeks, depending upon the route and animals used.

There are no outstanding agents used therapeutically which might contain the carcinogenics other than the tars and the oil of tar which is a distillation product of pine tar. The prepared coal tar of the British Pharmacopœia might be considered to be more dangerous from the carcinogenic viewpoint. The wood tars to date have not been incriminated but their use might well be questioned now that other substances are available Sollman (16). In instances where tar is to be used for therapeutic purposes, and especially if it be coal tar, then resort should be had to the tests for the presence of carcinogenics. The most promising test presented is that of the absorption spectra, as used by Lorenz and Shear (17). Color reactions with *p*-nitro-benzenediazonium chloride are mentioned by Fieser (*loc. cit.*) but it is noted that this test gives questionable results with 1:2:5:6 dibenzanthracene, the 10-methyl and ethyl derivatives of cholanthrene, with 5,10-dimethyl-1,2-benzanthracene and with 3-methyl-1,2-benzanthracene, all of which are carcinogenic. Phenols and amines must be removed previous to the chemical test also as they interfere. The biological assay method is finally the certain method of detection although the time factor is an obstacle here, whether the tar itself or extracts of it are employed. Eventually appropriate organic solvents may be found to extract the carcinogenics from tars for therapeutic uses; at present, however, alcohol, benzene, chloroform and petroleum ether all dissolve one or more of the known carcinogenics from coal tar. It is questionable whether bituminous shale products which are commonly sulfonated before use, contain carcinogenic substances. No researches have been conducted on this question as yet but undoubtedly such studies will be initiated in the future.

SUMMARY

1. A consideration of the chemical carcinogenics is presented with special reference to therapeutic use of agents that might possibly contain these agents.

2. It is suggested that appropriate tests of the medicinal tars and related products be made for the carcinogenics before these substances are recommended for therapeutic use.

3. The available tests for carcinogenics including the chemical, biological and physical (spectra) are discussed as to their efficiency.

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Book Reviews

Laboratory Exercises in the Chemistry of Medicinal Products, by WALTER H. HARTUNG, Ph.D., Professor of Pharmaceutical Chemistry, University of Maryland, W. TAYLOR SUMERFORD, Ph.D., Professor of Pharmaceutical Chemistry, University of Georgia, and MELVIN F. W. DUNKER, Ph.D., Fellow in Chemistry, Northwestern University. 152 pages, mimeographed by the University of Georgia Press. Price, $2.75.

This laboratory manual is intended for advanced undergraduate and beginning graduate students in pharmaceutical chemistry. The discussion, questions and experiments are designed to develop in the students a capacity to appreciate and understand better the principles on which medicinal and pharmaceutical chemistry are based. Wherever practicable, the experiments are carried out on the semimicro scale. The work is grouped in sixteen chapters headed as follows: Hydrocarbons, Halogenated Hydrocarbons, The Hydroxyl Group, Hydroxyl and Halogen Derivatives, Ethers, The Carboxyl Group, The Carbonyl Group, Nitrogen Compounds, Sulfur Compounds, Organometallic Compounds, Spot Tests, Library Problem, The Chromatograph, Dyes, Enzymes, Glycosides, Saponins, Tannins, Resins and Dialysis.—A. G. D.

Modern Drugs in General Practice, by ETHEL BROWNING. vii + 236 pages. $5^3/_8$ x $8^1/_2$. 1940. Baltimore: Williams & Wilkins Co. $3.00.

This book is intended to bring the general practitioner up to date with regard to the advances in medical sciences made in recent years. It aims to accomplish this purpose by discussing from a therapeutic viewpoint a selected group of drugs which, in the opinion of the author, are the most valuable. The sulfonamide group, gold salts, cardiac drugs, adrenergic and cholinergic drugs, hypnotics and diuretics are among the more important classes of drugs discussed. While the book is intended primarily for the practicing physician, it contains much information on the newer remedies which the pharmacists will find helpful.—A. G. D.

The Manuscript—A Guide for Its Preparation with Instructions for Handling Proof, by SAMUEL E. NORRIS, Compiler. 3rd Edition. xvi + 75 pages. 1941. New York: John Wiley & Sons, Inc. $1.00.

This small volume is intended primarily for authors who are writing for Wiley & Sons, but it contains much information of value to any author. Part I describes preparation and illustration of the manuscript, including copy for the offset process. Part II discusses the handling of galley and page proofs and plate proofs. The book makes no pretense of being a style manual, but it contains practical suggestions on capitalization, punctuation, abbreviations, compounding of words, citation of references and preparation of indexes. It also contains a section on "Poor Usage That Is Common" in which the correct uses of a number of words and phrases are illustrated. The book is believed to be worthy of a place in the libraries of all authors and editors.—A. G. D.

Food Analysis, by A. G. WOODMAN, xii + 607 pages. McGraw-Hill Book Co., Inc., 330 West 42nd St., New York, N. Y., and London, England, 1941. Price, $4.00.

This new edition is an improvement over previous editions in appearance due to the use of a better grade of paper and to wider margins on the page. The book would seem to have use as a brief manual for beginners in food chemistry. The more complex chemical procedures used by food analysts are mentioned by reference only. References to the literature are given at the ends of the chapters as in previous editions. Under food colors, there has been added a discussion of the new permitted dyes, including certain oil-soluble colors. The space given in previous editions to chemical preservatives has been reduced. There has also been added a discussion of the spectrophotometer in its relations to food analysis —A. G. D.