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PROCEEDINGS OF THE CANCER PREVENTION COMMITTEE

THIS committee is devoted to the study of environmental factors in cancer. The proceedings published herewith are records or abstracts of lectures and discussions bearing on this subject. The views expressed are those of the individual authors and do not necessarily represent the views of the committee as a whole. The membership is composed of individuals from universities, industries, insurance companies, and public health services interested in environmental, particularly occupational, tumor problems. The committee is incorporated as a nonprofit organization in the State of New York. Meetings are held at the Department of Industrial Medicine, New York University Post-Graduate Medical School. Communications should be addressed to the Secretary, William E. Smith, M.D., 477 First Ave., New York 16.

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SURVEY OF SOME CURRENT BRITISH AND EUROPEAN STUDIES OF OCCUPATIONAL TUMOR PROBLEMS

WILLIAM E. SMITH, M.D.
NEW YORK

ON JUNE 28, 1950, I sailed from New York with the object of visiting individuals engaged in the study of occupational tumor problems abroad. Experience gained from these visits provides the material of this report and will be presented under the following headings:

I. Shale Oil
II. Petroleum
III. Asbestos
IV. Dyestuffs
V. Sources of Statistical Data on Occupational Factors in Cancer.

I. SHALE OIL

Skin cancers in paraffin workers in the Scottish shale-oil industry were noted as long ago as 1876. In 1923, a detailed study of this problem with a report of 65 cases was prepared by Dr. Alexander Scott [1] at the request of the Scottish shale-oil industry. Dr. Scott has continued since that time to serve as medical consultant for the industry and as works physician. I had the privilege of visiting him at the Pumpherston Works in Mid-Calder, Scotland, where I also had the pleasure of meeting Mr. Alan Anderson, the works manager, Dr. E. Smith, the chief chemist, and Mr. Crombie, works chemist. Mr. Crombie gave me a tour of the plant. He stated that oil shale, the material taken out of the earth, is retorted at 1600 to 1900 F. at four plants in Scotland to yield naphtha, ammonia, and crude oil. The products are then sent to the Pumpherston Works, where they are processed to yield gasoline, industrial naphthas, paraffin, diesel oil, coke, and acid sludge.[2] The paraffin is obtained by a pressing operation, to be commented on in more detail later.

Presented at a meeting of the Cancer Prevention Committee in New York, Oct. 18, 1950.

Dr. Smith is Assistant Professor, Department of Industrial Medicine, Post-Graduate Medical School, New York University.

Travel expenses involved in the preparation of this survey were met by grants from the Anna Fuller Fund and from New York University.

1. Scott, A.: On the Occupation Cancer of the Paraffin and Oil Workers of the Scottish Shale Oil Industry, British M. J. 2:1108-1109 (Dec. 9) 1922; The Occupation Dermatoses of the Paraffin Workers of the Scottish Shale Oil Industry, with a Description of the System Adopted and the Results Obtained at the Periodic Examinations of These Workmen, Eighth Scientific Report, Imperial Cancer Research Fund, London, 1923, pp. 1-94; Shale Oil Industry in Occupation and Health, Report No. 242, International Labour Office, Geneva, 1925.

2. A Brief Description of the Operations of the Scottish Shale Oil Industry, Scottish Oils, Ltd., Glasgow, 1948. (32 pp.)

During the past 30 years the number of employees engaged in paraffin process work has remained about the same, 40 to 45. Dr. Scott stated that in 1919, when he made his first survey of the plant, 43% of the men in the paraffin works had dermatitis. At present, only 7.5% are so affected, representing a total of three cases, which I saw together with a fourth case, that of a man who had retired. All had been exposed for 20 years or more:

CASE 1 (Dermatitis Erythematosa).—The forearms were covered with dull-red splotches of varying size and shape, which blanched on pressure. This man had been employed for 27 years. The erythema had appeared over the past six months.

CASE 2 (Dermatitis Erythematosa).—This was a more advanced stage of the condition seen in Case 1. The splotches were raised and had a brownish tint. Between them were many white scars, the remains of earlier lesions. This man also had oil folliculitis, the hair follicles on the arms and over the knees standing out prominently as black points. He had been employed for 30 years. His dermatitis had begun 20 years ago.

CASE 3 (Dermatitis Papulare).—Brownish purple papules were scattered over the forearms. They were scaly and firm. The man had been employed for 24 years. Lesions began to appear 10 years ago.

CASE 4 (Epithelioma).—Two cancers had been removed from this man's forearms. He had four keratotic horns on his hands and a suspiciously firm mound in the skin at the wrist. The skin over this mound did not seem remarkable, and the lesion had no papillomatous features, but Dr. Scott said he had found cancerous downgrowths in a biopsy specimen of such a lesion from an earlier patient. On the anterior surface of the legs and on the forearms there was a fading dermatitis erythematosa. On both the legs and the arms were many "paraffin warts." The latter were raised, conical, red with a black head in the top. They were said to be due to obstruction of sebaceous ducts with paraffin, and to disappear readily when this was expressed. They were not associated with subsequent neoplastic change. This man had been employed in the paraffin works for 30 years and had then retired. His dermatitis and subsequent skin tumors had developed wholly in the period of three years after he left the works. Dr. Scott emphasized this case as illustrating the need to follow exposed personnel even though they may have ceased to be employed in a hazardous job.

All men at the works are examined at three-month intervals, and any skin abnormalities are recorded on charts of the anterior and posterior body surfaces. In this way, Dr. Scott has been able to show that in paraffin workers tumors arise in areas of skin that have been the site of preexisting dermatitis. By contrast, in oil workers epitheliomas usually arise without preexisting dermatitis, even on hands or arms. The records disclosed no association between injuries and localization of tumors.

The erythematous dermatitis may occur after only a few days of employment in the paraffin works. It usually responds to treatment. If it persists, the man is removed from the works, the dermatitis then usually clearing up. If the dermatitis is allowed to become chronic, with the skin becoming indurated and covered with scaly or papular lesions, danger of cancer arises. In contrast to the tendency for paraffin workers' cancer to occur on the forearms, oil workers, retortmen, and laborers more commonly incur scrotal cancer, which arises without observable preexisting dermatitis.

On the basis of the greatly decreased incidence of dermatitis and skin tumors experienced among employees in recent years Dr. Scott felt that these problems had been brought under satisfactory control in the Scottish shale-oil industry. In the case of the paraffin workers, he felt this improvement had been made possible in large measure by a change in the type of press, a change made in 1935. Prior to that date the crude paraffin scale from a low-pressure pressing operation was

shoveled onto canvas sheets, on which it was spread out into a shallow layer by the workers' bare hands. The sheets, thus loaded, were piled one on top of the other, by hand, into a press to squeeze out the oil, after which the paraffin was flaked off by hand. The whole process thus involved very intimate exposure of the skin of the forearms, but the legs and the body were protected by heavy canvas wrappings and aprons, respectively. These conditions doubtless accounted for the common occurrence of skin tumors on the arms of paraffin workers and the relative rarity of scrotal cancers. Leather or rubber shields had been experimented with, to protect legs and body, but discarded in favor of canvas, which was found in practice to be more effective in preventing dermatitis. The canvas is of the same quality and thickness as that ordinarily used in wax presses (16 oz. per square yard; 54 gm. per square meter). In 1935, the procedure just described was replaced by high-pressure filter presses into which the oil is fed, chilled, and pressed without handling until the press is opened. The pressmen wear canvas aprons. I saw these new presses and found them to be very similar to those in use in American waxworks. Since skin and scrotal cancers have occurred in pressmen operating such machines in America, it did not seem likely that the change in equipment could account entirely for the very remarkable decrease in skin disorders described by Dr. Scott, though it must have been a very major step in that direction. Other factors have also to be considered.

Among these other factors has been the installation of shower baths and washing facilities. Ordinary neutral soap is used. The workers have cooperated in the use of these facilities, which include means for laundering their own work clothes, which they leave at the plant in lockers instead of wearing them home. For laundering clothes, a detergent ("by-prox") is used and has been found satisfactory in removing oily matter. It is made by Scottish Oils, Ltd., Mid-Calder, Scotland, and is a sodium alkyl sulfate (a sulfated oil, not a sulfonated oil). A further procedure has been adopted based on experiments by the Tworts,[3] who found that mice painted with carcinogenic oils yielded fewer tumors if their skins were rubbed with hydrous wool fat (lanolin) prior to painting. At the Pumpherston works, each man is issued a weekly ration of ½ lb. (226.5 gm.) of olive oil containing 25% hydrous wool fat. Peanut oil had been tested for this purpose but discarded as not having enough "cling"; i. e., it remained on the skin less well than olive oil. Castor oil had been used earlier, without hydrous wool fat, and given up for reasons not stated. At present, therefore, the practice is for the men to rub their arms and hands well each morning with the mixture of 25% hydrous wool fat in olive oil. Aside from any merit which this procedure may have in protecting the skin, it is said to facilitate the removing of oil from the skin by subsequent washing with ordinary soap and water. Barrier creams ("rozalex" and "esoban") have also proved satisfactory. If dermatitis develops, it is treated with a medicated cream.[4] This alleviates the

3. Twort, C. C., and Twort, J. M.: Studien über Krebsentstehung, Ztschr. Krebsforsch. **32**:504, 1930. Twort, J. M., and Lyth, R.: The Prophylactic Effect of a Colloid Material on the Skins of Mice Painted with Various Types of Carcinogenic Agents, J. Hyg. **43**:252-255. 1944.

4. This cream is made of the following ingredients: stearic acid, 15%; hydrous wool fat, 10%; white wax, 8%; liquid petrolatum, 16.5%; distilled water, 48%; beta-phenylethyl iodide, 1%; titanium dioxide, 0.5%; monoethanolamine, 2-aminoethanol, 0.8%; chlorocresol, 0.2%. It is marketed by Calmic Ltd., Crewe, England.

acuteness of the disease, and Dr. Scott finds that the acute type clears up readily. Once wartiness or scaliness develops, it will not clear up but can be kept under control by any good dermatitis cream.

In addition to the change in equipment and the measures just described for protecting the skin, potential employees are screened with the aim of picking men with swarthy skins, as these do not appear as susceptible to oil irritation. Men with auburn hair and men who freckle readily or who have preexisting skin disease, especially psoriasis, are not hired as pressmen.

Lastly, I could not fail to note the excellent relationships between management, labor, and medical officer. Their mutual interest and cooperation have no doubt been a major factor in bringing the situation under control. The friendly confidence apparent in the relations between the employees and Dr. Scott is a warm tribute to this kindly physician and to the officials of the company, who have together ably met a classic task of industrial medicine. It is a pleasure to acknowledge the courtesy and advice of Mr. Alan Anderson, the works manager.

Dr. Scott showed me an excellent series of lantern slides illustrating gross and microscopic features of the dermatitis and the tumors here discussed. The Cancer Prevention Committee has obtained reproductions of these slides, which are available for loan to oil companies wishing to use them for instruction of medical personnel.

In London, I visited Dr. S. A. Henry, former medical inspector of factories, who has analyzed 4,624 cases of skin tumors reported as of occupational origin since 1920 under the British Workmen's Compensation Act, provisions of which are described in Dr. Henry's reports.[5] Mule spinners in the cotton textile industry contributed 1,407 of the above total of cases. The hazard in this occupation has been traced to the use of carcinogenic oils, notably those containing shale oil, to lubricate the spindles. Dr. Henry's published analyses show a marked decrease of the skin cancers attributed to shale or mineral oils in recent years. He credited this improvement to increasing adoption of noncarcinogenic spindle oils and to the fitting of felt washers onto the mules to prevent oil spray. The shortest time elapsing from onset of work to manifestation of cancer in cases attributed to shale or mineral oil was four years, but the maximum number of cases was reported after 50 to 54 years' exposure. Further comment on this subject is contained in the last section of my report.

Extensive experimental studies on the carcinogenicity of shale and mineral oil are contained in the monumental works of the Tworts and their associates. Dr. C. C. Twort has now retired from work with oils, but he generously supplied at my request a collection of his papers on the subject. A bibliography of this valuable collection, comprising some 40 titles, can be obtained from the Cancer Prevention Committee.

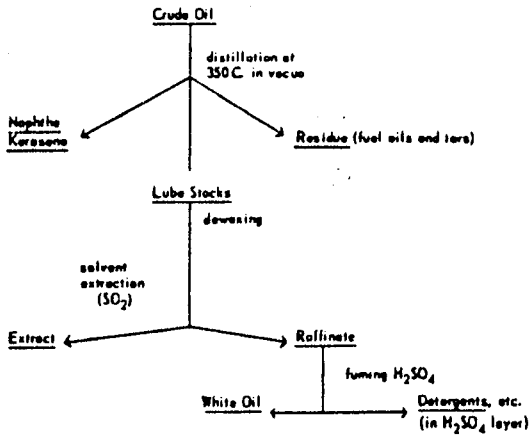
II. PETROLEUM

Through the courtesy of Prof. John R. Squire, I had the opportunity of becoming acquainted with the studies going forward at Birmingham University in collaboration with the Committee on Carcinogenic Action of Mineral Oils appointed

5. Henry, S. A.: (*a*) Occupational Cutaneous Cancer Attributable to Certain Chemicals in Industry, British M. Bull. **4**:389-401, 1947; (*b*) Cutaneous Cancer in Relation to Occupation, Ann. Roy. Coll. Surgeons England **7**:425-454, 1950.

by the Medical Research Council with the support of the British petroleum industry. In the cancer research laboratories of the University various oils are being tested on the skins of animals by Dr. D. L. Woodhouse, and epidemiological studies are pursued by Dr. C. N. D. Cruickshank and Dr. J. P. Bull under the direction of Prof. Squire in the Medical Research Council Industrial Medicine Research Unit in the nearby Birmingham Accident Hospital. Oil samples for experimental study are being prepared in the department of chemical engineering at Birmingham University under the direction of Prof. F. H. Garner. These British studies, like those conducted by ourselves [6] at New York University, are concerned with oils derived from petroleum rather than from oil shale. Important differences emerged between the studies in progress in England and those in New York, for the British are testing lubricating oils where cracking is avoided whereas we have been concerned primarily with cracked oils designed for other purposes.

Prof. Garner stated that British lubricating oils are made by subjecting crude oil *in vacuo* to distillation at a temperature not over 350 C. This is the actual tem-



Outline of a petroleum fractionation.

perature *in vacuo,* not after conversion to atmospheric pressure. The vacuum is about 20 mm., hence this temperature would correspond to about 550 C. (1,000 F.) at atmospheric pressure. Prof. Garner stated that in practice the oil is exposed to this temperature only for a matter of minutes and that the refineries try to avoid cracking by keeping the time of exposure down as much as possible and trying to keep the *in vacuo* temperature below 300 C. The accompanying outline may serve for orientation.

The SO_2 extract (Edeleanu process) removes the aromatics, which are undesirable in lubricating oils because they oxidize easily and are then deposited as sludge. The extracts are said to be used to some extent in cutting oils and in the rubber industry. The raffinate (oil left after SO_2 extraction) is used for lubricating purposes in the engineering industry. When raffinate is treated with fuming

6. Smith, W. E.; Sunderland, D. A., and Sugiura, K.: Experimental Analysis of the Carcinogenic Activity of Certain Petroleum Products, A. M. A. Arch. Indust. Hyg. 4:299-314 (Oct.) 1951. Sunderland, D. A.; Smith, W. E., and Sugiura, K.: The Pathology and Growth Behavior of Experimental Tumors Induced by Certain Petroleum Products, Cancer 4:1232-1245 (Nov.) 1951.

sulfuric acid, white oil is obtained, and this is now used to lubricate spindles in the cotton textile industry in place of the shale oil long associated with mule spinners' cancer.

Biological tests carried out on mice by Dr. Woodhouse demonstrated varying degrees of carcinogenicity in several lube distillates, residues, and one extract.[7] Six finished spindle oils (not white oils) were tested, and all exhibited some degree of carcinogenicity for mice. In 1946 tests were conducted with 10 oils, each on a group of 50 mice (25 males, 25 females). In 1947 these tests were repeated. A statistical analysis of the results was made by Dr. J. O. Irwin and is appended to Dr. Woodhouse's paper.[7] The two sets of tests demonstrated that groups of 50 mice could be counted on to give satisfactory impressions of the carcinogenicity of a sample for ordinary purposes. That is, no sample found weak in one year proved potent the next, or vice versa. If a close comparison of the carcinogenicity of different samples with attention to small differences is desired, they should be tested concurrently.

The British group is exploring means for evaluating the carcinogenicity of oils by chemical or physical methods rather than by time-consuming biological tests. The earlier work on this subject by C. C. and J. M. Twort and their colleagues was reviewed by Irwin and Goodman,[8] who presented arguments to show that refractivity per se is as good a measure of carcinogenicity as the study of the change in refractive index following intraperitoneal injection (see Paragraph 9 in the summary of their paper). The matter was further discussed by S. J. M. Auld.[9] Col. Auld stated that certain blending procedures render refractive-index studies meaningless as measures of carcinogenicity and presented data illustrating this point. The present position of the British Committee on Carcinogenic Action of Mineral Oils is that there is no reliable means for estimating the carcinogenicity of oils aside from the biologic test. Perhaps an exception to this statement may be made in the matter of color in the sense that white oil has never been found to be carcinogenic. Addendum: Chemical and physical methods for estimating the carcinogenicity of high-boiling petroleum products have recently been developed at the Standard Oil Development Company, Linden, N. J., utilizing biologic test data supplied by our laboratory at New York University.[9a]

The question of a solvent less volatile than acetone or benzene often arises in experimental cancer work. Dr. Woodhouse has found toluene satisfactory. He states that it is no more irritating to mouse skin than acetone or benzene and is less hard on the animal as a whole than is benzene. He has used toluene to dilute or dissolve heavy oils or tars with satisfactory results as regards skin tests of these substances for carcinogenicity. Dr. Woodhouse found, as have others, that tumors arise less quickly and in less number when a carcinogen is applied in white oil rather than in acetone and has obtained quantitative results in relation to the dilu-

7. Woodhouse, D. L.: The Carcinogenic Activity of Some Petroleum Fractions and Extracts, J. Hyg. **47**:121-134, 1950.

8. Irwin, J. O., and Goodman, N.: Statistical Treatment of Measurements of Carcinogenic Properties of Tars and Mineral Oils, J. Hyg. **44**:362-420, 1946.

9. Auld, S. J. M.: Environmental Cancer and Petroleum, J. Inst. Petroleum **36**:244, 1950.

9a. Fischer, H. G. M.; Priestley, W., Jr.; Eby, L. T.; Wanless, G. G., and Rehner, J., Jr.: Properties of High-Boiling Petroleum Products: Physical and Chemical Properties as Related to Carcinogenic Activity, A. M. A. Arch. Indust. Hyg. **4**:315-324 (Oct.) 1951.

tion used. Mite and flea infestations present serious problems in experiments on the mouse skin, and investigators often hesitate to use insecticides for fear of introducing unknown factors into their experiments. Dr. Woodhouse uses benzene hexachloride for control of these pests, mixing a little of the powder into the sawdust used for bedding. Tests conducted by himself and Prof. Orr at Birmingham have shown that this material does not produce cutaneous injury, skin tumors, or pulmonary adenomas in mice. The preparation they use contains 0.1% by weight benzene hexachloride mixed with talc.[10]

Dr. Woodhouse has studied means for removing carcinogenic oils from the skin of mice, using ultraviolet fluorescence as the criterion. He found that all fluorescence could be removed from the skin by wiping the painted area with cotton soaked in white oil, then wiping the white oil off with dry cotton. Sulfonated castor oil proved less effective for this purpose. White oil did not injure the skin of mice, even when applied twice a week for 25 weeks. In our hands this procedure has not completely removed fluorescence from mouse skins painted with high-boiling catalytically cracked oil.

I next visited Dr. C. N. D. Cruickshank and Dr. J. P. Bull at the Birmingham Accident Hospital. Dr. Cruickshank recently published an experimental study of various skin cleansers, concluding that oils could best be removed from the human skin by a mixture of equal parts of soap powder and fine wood flour.[11] He has subsequently found white oil to be more efficient than the mixture of soap and wood flour. His experiments showed that barrier creams were of little value as protection against oil, but he felt that an emollient cream to minimize the deleterious effects of frequent skin cleansing was useful. A practical discussion of skin cleansing in industry with special reference to oil is contained in another paper by Dr. Cruickshank,[12] which states that during the years 1943 to 1946 approximately 9,800 cases of industrial dermatitis (all causes) were certified annually in Britain with an estimated annual loss of 98,000 man-weeks. It is interesting to note that in the two years 1943 and 1944 in New York State the claims made for industrial dermatoses totaled 4,135, of which 890, or 21.5%, were for dermatoses attributed to oil or grease exposures. Half of the latter group involved cutting oils.[13] The Birmingham workers have also been engaged in statistical studies of the types and number of industrial dermatoses notified in Britain.[14]

Dr. Cruickshank gave me a striking demonstration of his method of removing a lubricating oil from the human skin. He painted this oil on his arm, which came to fluoresce brilliantly in ultraviolet rays. After washing with the mixture of soap and wood flour and water, the diffuse fluorescence was seen to have been removed, but the hair follicles in the oiled area shone forth brilliantly as fluorescent spots.

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10. It is marketed under the name "lorexane" by the Pharmaceutical Division of Imperial Chemical Industries, Manchester, England. Another preparation of "lorexane," 5% in miscible oil, is also available commercially and is used at Birmingham as a spray to control flies on walls and in boxes.

11. Cruickshank, C. N. D.: The Evaluation of Skin Cleansers and Protective Creams for Workmen Exposed to Mineral Oil, British J. Indust. Med. 5:204-212, 1948.

12. Cruickshank, C. N. D.: Industrial Skin Disease, Nursing Times, July, 1949.

13. Shapiro, H.: Cutting Oil Dermatoses, Month. Rev., New York State Dept. of Labor 20:5-8 (Feb.) 1950.

14. A review of occupational skin diseases by Squire, Cruickshank, and Topley recently appeared in the *British Medical Bulletin* (7:28-41, 1950).

He then covered his arm again with the lubricating oil, but this time rubbed it off with cotton soaked in a colorless technical grade of white oil. Almost all the fluorescence was thus removed, only a little remaining in a very few scattered hair follicles. Dr. Cruickshank stated that he had not found dermatitis to result in human skin washed repeatedly with white oil, provided the skin was healthy to start with. Cases of irritation occurred when the oil was applied under dressings. Further discussion of ways to protect the skin against oils is contained in my section on "Shale Oil."

Dr. Cruickshank and Prof. Squire have described warts that occurred on the skin of 33% of a group of 138 machine-tool operators exposed to sprays of a cutting oil which they found capable of inducing skin tumors in animals.[15] I had an opportunity to examine many excellent photographs of these men. Some of the lesions were flat, white keratoses; others were raised, rugose, and pigmented. Histological sections showed the latter to be papillomas. One man had a scrotal cancer, sections of which I saw. Photographs of his arms showed half a dozen small papillomas.

Prof. J. W. Cook, at the University of Glasgow, is attempting to identify the chemical nature of the carcinogens in the petroleum oils under biologic test at Birmingham. Prof. Cook was away from Glasgow when I visited his laboratory, but the work was described to me by his assistant, Dr. W. Carruthers. By high-vacuum distillation, chromatography on alumina, and purification with picric acid, they have isolated a chrysene with a long aliphatic side chain. Their general procedure is to extract the oils with sulfur dioxide, run the extracts through alumina columns, and elute with petroleum benzin. They have thus obtained four crystalline compounds, as yet unidentified, of which two are aromatic. Only one has been obtained in sufficient quantity for biologic test, but results are not yet at hand.

They have failed to find benzpyrene. The method of search was to extract the aromatics with sulfuric acid, regenerate the hydrocarbons, and examine by fluorescence spectroscopy. Dr. I. Hieger, of the Chester Beatty Institute, London, was also said to have searched unsuccessfully for benzpyrene in lube oils found carcinogenic at Birmingham. I may note here that a very simple procedure for the detection of benzpyrene was demonstrated to me by Mr. Robert Waller in Sir Ernest Kennaway's laboratory in London. An account of this method will appear shortly in the *British Journal of Cancer*. All parties agreed that absorption spectroscopy was useless as a means of identifying compounds in complex mixtures, such as oils, and emphasized the need for fluorescence spectroscopy.

III. ASBESTOS

The 1947 report of the Chief Inspector of Factories[16] noted the presence of cancer of the lungs or the pleura in 31 (13.2%) of 235 cases of asbestosis recorded in the 23 years from 1924 through 1946. These figures stimulated interest in the question of whether lung cancer is an occupational hazard in the asbestos industry, and, if so, which phases of the industry and what working conditions present such a hazard. The data cited above were prepared by the Senior Medical Inspector of Factories, Dr. E. R. A. Merewether, whom I visited.

15. Cruickshank, C. N. D., and Squire, J. R.: Skin Cancer in the Engineering Industry from the Use of Mineral Oil, Brit. J. Indust. Med. 7:1-11, 1950.

16. Annual Report of the Chief Inspector of Factories for the Year 1947, London, His Majesty's Stationery Office, 1948, pp. 79 to 81. (Price 3 shillings.)

Dr. Merewether referred to the governmental report published in 1930 by himself and C. W. Price.[17a] This report showed that asbestosis developed in 80% of men employed 20 or more years in the industry [17b] and that in various groups of workers the percentage in which asbestosis developed varied directly with the dustiness of the process in which the groups were engaged.[17c] These findings led to the adoption of laws requiring ventilation of asbestos work rooms in Great Britain (Asbestos Industry Regulations, 1931). Detailed specifications for safety equipment are contained in Factory Orders, 1944. It should be noted that there is no mining of asbestos in England. Hence, the British figures refer only to individuals engaged in weaving or other manufacturing or handling operations.

A first problem was whether the apparent association of lung cancer and asbestosis means merely that workmen's compensation procedures funneled all chest diseases into one group. This possibility cannot be supported, however, for no such high incidence of lung cancer has been found in cases of silicosis, which are likewise reported to and reviewed by the Pneumoconiosis Board. Cancer of the lungs or the pleura was noted in only 91 (1.32%) of 6,884 cases of silicosis recorded from 1930 through 1946.[18] The incidence of cancer was thus 10 times greater in asbestotic lungs than in silicotic lungs. Data on the average age at death in this silicotic group were not given, but the same report listed a series of 1,037 silicotics who died at an average age of 58.2 years, compared with a group of 160 asbestotics who died at an average age of 47.5 years. Therefore, the difference in cancer incidence in the two diseases could not be attributed to death of silicotics before they reached the "cancer age"; in fact, the silicotics would appear to have had greater opportunity by a full decade to yield cancers. Similarly, the average duration of employment in these two groups could not account for the difference: 34.3 years for the silicotics against 14.9 years for the asbestotics.

A measure of the rate at which lung cancer occurs in the general population of England and Wales can be found in the Registrar General's Statistical Review (1949). Employing the data given on pages 3 and 145 of the Review, one can calculate that 1.36% of all deaths in the three years from 1943 to 1945 were reported as due to cancer of the lung, the bronchus, or the pleura. It is of interest to note that the percentage of deaths attributed to lung cancer in the general population is almost identical with the figure of 1.32% for the finding of lung cancer in a large group of silicotic lungs.

Documentation of the cases of coexistent lung cancer and asbestosis became my next endeavor. For this purpose, I visited Dr. S. Roodhouse Gloyne at the Institute for Social Medicine in Oxford. Dr. Gloyne's studies of the pathology of asbestosis are well known.[18] For many years he has received lungs for review on matters of compensation. Dr. Gloyne generously gave me permission to cite the data in Table 1, which he assembled from lungs that he personally examined in the gross and microscopically. It is to be hoped that a full account of them will be

17. (*a*) Merewether, E. R. A., and Price, C. W.: Report on Effects of Asbestos Dust on the Lungs and Dust Suppression in the Asbestos Industry, London, His Majesty's Stationery Office, 1930 (summarized in J. Indust. Hyg. & Toxicol. **12**:117, 1930, and in Tubercle **15**:69-81, 109-118, and 152-159, 1933-1934); (*b*) ibid., p. 10, Table 3; (*c*) ibid., p. 14, Table 7.

18. Gloyne, S.: The Morbid Anatomy and Histology of Asbestosis, Tubercle **14**:445-451, 493-497, and 550-558, 1932-1933; Asbestosis, in Silicosis and Asbestosis, edited by Lanza, A. J., New York, Oxford University Press, 1938, pp. 225-244.

published from a manuscript that was in preparation at the time of his recent death.[19]

In addition to the material of Table 1, Dr. Gloyne also examined the lungs of 169 persons without pneumoconiosis but employed in the same set of industries as those included in Table 1. Among these, he found 14 who had primary lung cancer (8.3%). The lungs of 11 asbestos workers who had no asbestosis (either in the gross or microscopically) were negative for carcinoma. The 17 cases of cancer in asbestotic lungs (Table 1) were about equally distributed between men and women (10 men, 7 women), whereas in the normal population in England the ratio is said to be 4 men to every woman with cancer of the lungs. In addition to the higher incidence of cancer in asbestotic lungs, Dr. Gloyne felt that this difference in the sex ratio afforded evidence for an occupational factor.

It will be apparent that the lung cancer rate of 8.3% found in the 169 individuals without pneumoconiosis and the rates of 5.1 to 8.9% in the groups with pneumoconioses other than asbestosis are much higher than the rate of 1.36% estimated for the general population on the basis of death certificates and the rate of 1.32% found from pathological examination of the large group of silicotics previously

TABLE 1.—*Incidence of Primary Lung Cancer in Groups with Various Types of Pneumoconiosis (Data of S. Roodhouse Gloyne)*

Occupational Group	Persons with Pneumoconiosis		
	Total Number	Number with Primary Lung Cancer	Percentage with Primary Lung Cancer
Iron and steel workers	78	4	5.1
Pottery workers	340	19	5.6
Coal miners	293	19	6.5
Stonemasons	90	8	8.9
Asbestos workers	121	17	14.0

described. It is thus probable that the higher rates reflect closer study. Despite this elevation of the base line for comparison, the rate in the asbestosis group continued to stand out. Dr. Gloyne stated that of the total number of lung cancers in his series, 7.5% were discovered only on microscopic examination. These were scattered through the various groups.

The type of cancer[20] and the degree of asbestosis in the 17 cases of the asbestosis group are given in Table 2. Only one individual (M. S.) had evidence of tuberculosis. In the 922 cases comprising the whole of the pneumoconiosis group (Table 1), 20% showed tuberculosis. Dr. Gloyne made a special search for precancerous changes in asbestotic lungs and did not detect any. Desquamation of bronchial epithelium was occasionally seen, but squamous cell metaplasia was not found save in the cancers themselves. It will be noted from Table 2 that the degree

19. A brief posthumous publication has appeared (Gloyne, S. R.: Pneumoconiosis: A Histological Survey of Necropsy Material in 1,205 Cases, Lancet 1:810-813, 1951).

20. Through the courtesy of Dr. K. F. W. Hinson, of the London Chest Hospital, we have received lobes from six lungs of Dr. Gloyne's series. This material was examined by Dr. Douglas A. Sunderland, of Memorial Hospital, New York. Two cases (C. W. and J. W.) classified as squamous cell cancer by Dr. Gloyne were interpreted as terminal bronchiolar ("alveolar cell") carcinoma by Dr. Sunderland.

of asbestosis in the group of cancerous lungs was recorded as "moderate" or "extensive" in every case except one, where it was "mild." The estimation of the degree of asbestosis was made in every instance by the same observer (Dr. Gloyne).

The 17 cases of coexistent lung cancer and asbestosis studied by Dr. Gloyne were assembled over a period of 20 years (1929 to 1949). All had their exposure to asbestos prior to 1932, the year modern exhaust ventilation devices were adopted in conformance with government regulations. The majority were employed at a plant handling Rhodesian blue and South African (also blue) asbestos. Both these types are more brittle than Canadian white asbestos, hence give rise to more dust. At least one patient (J. I.), however, was stated to have been exposed only to Canadian white asbestos.

I next visited Prof. E. J. King at the British Post-Graduate Medical School in London, where I had the opportunity to examine protocols relating to the lungs

TABLE 2.—*Pathological Findings in 10 Men and 7 Women with Asbestosis and Lung Cancer (Data of S. Roodhouse Gloyne)*

Patient	Degree of Asbestosis	Type of Cancer
(Males)		
A. G.	Extensive	"Oat Cell"
A. W.	Extensive	"Oat Cell"
P. B.	Moderate	Squamous Cell
J. G.	Moderate	Squamous Cell
J. I.	Moderate	Squamous Cell
G. M.	Moderate	Squamous Cell
E. T.	Moderate	Squamous Cell
J. W.	Moderate	Squamous Cell
C. W.	Moderate	Squamous Cell
J. P.	Mild	"Oat Cell"
(Females)		
Li. S.	Extensive	Squamous Cell
L. W.	Extensive	Squamous Cell
M. C.	Moderate	Squamous Cell
E. O.	Moderate	Squamous Cell
M. S.	Moderate	"Oat Cell"
Le. S.	Moderate	"Oat Cell"
E. M.	Moderate	Adenocarcinoma

of 11 individuals who had been employed in a plant using Canadian white asbestos. The pathological descriptions were made by Dr. C. V. Harrison. Varying degrees of asbestosis were noted in 8 of these 11 lungs; there were 3 cancers, all among the 8 asbestotic lungs. An "oat cell" cancer was found in lungs of one patient (male) with extensive asbestosis. Anaplastic carcinomas were described in two patients (males), in one of whom the degree of asbestosis was moderate; in the other the asbestosis was minimal. The asbestosis ranged from extensive to moderate in the 5 remaining patients in whom this disease was not complicated by cancer. Combining the data of Dr. Gloyne and Dr. Harrison, one finds that in 20 cases of coexistent lung cancer and asbestosis, the degree of asbestosis was "extensive" in 5, "moderate" in 13, and "mild" or "minimal" in 2. The cancer was squamous cell in 11, "oat cell" in 6, anaplastic in 2, and adenocarcinoma in 1. There was no correlation between type of cancer and degree of asbestosis.

I next visited Dr. Hubert Wyers, the medical officer for a company in England engaged in manufacturing asbestos products from blue asbestos mined in Rhodesia

or South Africa. Dr Wyers is the author of a valuable clinical study of asbestosis.[21] He stated that asbestosis was recognized in 1900 and that the industry grew to major stature in the war of 1914-1918. Dr. Wyers has seen only two deaths from asbestosis in people who started to work in the industry after 1932, the year when exhaust ventilation devices were installed. In contrast, he had seen 115 deaths involving asbestosis in persons employed before 1932. He feels that the regulations in regard to safety conditions in the asbestos industry are therefore a great triumph of preventive medicine. The diminution in the severity of the disease in terms of the number of persons affected is further borne out by lessened severity in the individual cases. Prior to 1932 the disease was acute, with deaths sometimes occurring after two years of exposure. The disease as it is now seen is much more chronic. In the 117 cases of asbestosis seen by Dr. Wyers primary lung cancer was found in 17. Dr. Gloyne examined the lungs in these 17 cases, and his pathological diagnoses of the tumors have been given above.

All of the 17 individuals with asbestosis and lung cancer were exposed before 1932. According to Dr. Merewether, the additional 3 cancer patients studied by Dr. Harrison were likewise exposed before 1932. I specifically inquired of Dr. Merewether whether any cases of coexistent lung cancer and asbestosis had been reported in individuals whose exposure had taken place only since 1932. He stated that only one such case has been reported: that of a man employed in the industry between 1935 and 1945. This single case might well be expected as part of the "normal" incidence of lung cancer in any group as large as that employed in the asbestos industry.

In summary, then, I was able to find some information on a total of 21 persons with coexistent lung cancer and asbestosis, of whom only one was a man working under conditions now prevailing in the industry. The additional 10 patients making up the total of 31 described in the Annual Report of the Chief Inspector of Factories for the year 1947 had all been exposed prior to 1932 and I did not attempt to locate autopsy protocols describing them.

It was the consensus of Dr. Gloyne, Dr. Wyers, and Dr. Merewether that the nature of the disease, asbestosis, as seen in England has changed so that it is less common and less severe in individuals whose employment in the industry has taken place only since 1932. It was the consensus that a lung tumor hazard formerly existed in this industry in Great Britain but that there is no evidence to show that such a hazard continues to exist under the working conditions now prevailing.

It should be further noted that in the 1947 factory report Dr. Merewether shows that a mean exposure of 16.5 years, with a range of 1.5 to 40 years, existed in the cases of asbestos workers who succumbed to lung cancer. Individuals beginning their employment in the 1930's are therefore only now reaching the mean age at which tumors might be expected to appear. The size of this group is not known, but the fact that it has thus far provided only a single case of coexistent lung cancer and asbestosis argues that any lung tumor hazard has been greatly diminished, at least in point of time. Whether there will be any significant number of cases with delayed appearance remains to be seen.

Prof. King described his experimental studies on the use of alumina in pneumoconioses. In the case of experimental asbestosis, alumina had no beneficial effect

21. Wyers, H.: Asbestosis, Postgrad. M. J. 26:631-637, 1950.

in either of two series of tests. I examined histological sections of rat lungs that had received intratracheal instillations of asbestos fibers. Studies of these lungs have been published.[22] Prof. King stated that he had found no difference in the response of rat lungs to Canadian as contrasted with Rhodesian fibers, nor had any epithelial changes been evident. A few pulmonary adenomas were present in the slides shown me, but these tumors are known to occur spontaneously in rats and cannot be attributed to the instillation of asbestos fibers.

In regard to the animals chosen for experimental work, Dr. Gloyne stated that he had found rabbits and guinea pigs more susceptible to asbestosis than rats. He had not tested mice.

(See "Abstract of Discussion" at end of this paper for further comments on lung cancer in relation to asbestosis.)

IV. DYESTUFFS

In the light of the evidence that bladder tumors are caused by beta-naphthylamine in the dye-manufacturing industry, production of this chemical was reportedly discontinued as of April, 1950, by Imperial Chemical Industries and by the Clayton Aniline Company, the largest British dye producers. They are said now to make sulfonic acids by sulfonating beta-naphthol and aminating it later, thus avoiding the stage at which beta-naphthylamine is produced. This change in the manufacturing process should not only protect workers in the plants but also remove the potential hazard of distribution of free beta-naphthylamine as a contaminant of food dyes consumed by the public.

The question whether benzidine presents an occupational tumor hazard has long been debated. A recent paper by Barsotti and Vigliani presents an impressive series of cases of bladder tumors attributed to benzidine exposure in an Italian dye-works. It is claimed that a majority of the patients had not been exposed to beta-naphthylamine. A translation of this Italian study appears in an accompanying paper.[23]

Dr. Kenneth Baker, of the Clayton Aniline Company, Manchester, England, described experiments showing that benzidine itself is not carcinogenic but that men exposed to benzidine excrete in their urine a hydroxylated derivative, 3,3'-dihydroxy-4,4'-diaminodiphenyl, a compound which he demonstrated does evoke bladder tumors in mice.[24] Mice were given repeated subcutaneous injections of olive-oil suspensions of benzidine or of its hydroxylated derivative 3,3'-dihydroxy-4,4'-diaminodiphenyl. Nine mice were given the hydroxylated compound, and bladder papillomas developed in five and a bladder carcinoma in one. No bladder tumors were found in the mice given benzidine or in control animals given injections of olive oil alone.

Dr. Georgianna Bonser, Leeds University, England, kindly summarized for me the current work of her laboratory. The curious ability of beta-naphthylamine to call forth bladder tumors in man and in dogs but not in other species has led to the view that its carcinogenic action may depend on some metabolic change

22. King, E. J.; Clegg, J., and Rae, V.: Effect of Asbestos, and of Asbestos and Aluminium, on the Lungs of Rabbits, Thorax 1:188-197, 1946.

23. Barsotti, M., and Vigliani, E.: Bladder Lesions from Aromatic Amines, Med. lavoro 40:129-135 (for English translation see A. M. A. Arch. Indust. Hyg., this issue, pp. 234).

24. Baker, K.: The Carcinogenic Activity of Dihydroxy Benzidine, Acta Unio internat. contra cancrum 7(Pt. 1):46-51, 1950.

impressed on it in men and dogs. In Dr. Bonser's laboratory, the hydroxylated derivative, 1-amino-2-naphthol has been isolated from the urine of both men and dogs exposed to beta-naphthylamine. The conversion to 1-amino-2-naphthol occurs less readily in the cat, even less so in the rat. The mouse is less able to convert than the rat, and the rabbit less able than the mouse. 1-amino-2-naphthol is toxic and unstable and is being tested for carcinogenicity by use of its acetylated derivative. This derivative is being given to dogs and mice, species known to be capable of deacetylating it. They have failed to find 1-amino-6-naphthol in the urine of dogs, cats, rats, mice, or rabbits fed beta-naphthylamine.

Bladder tumors, in the dye industry, are often referred to as "aniline cancers." There is no convincing evidence that aniline itself is carcinogenic. Prof. Dr. Druckrey, of Freiburg, Germany, has recently reported experiments showing that aniline evoked no tumors when fed to rats.[25] Dr. Bonser stated that she had obtained similar negative results with dogs fed aniline for five years.

Oil orange E (commercial benzene-azo-β-naphthol [Sudan I]) has in recent years been introduced to color margarine in England, but Kirby and Peacock of the Royal Cancer Hospital, Glasgow, Scotland, have shown that this dye causes tumors in mice,[26] and its use in human foodstuffs has been discontinued.

At the Fifth International Cancer Congress in Paris, the German delegation introduced a resolution, accepted by the Congress, requesting the Union Internationale Contre le Cancer to collaborate with governments and industries for unification of regulations on coloring matters for foods from the point of view of potential cancer hazards.[27] To exemplify the purpose of this resolution: The potent carcinogen paradimethylaminoazobenzene ("butter yellow") is not permitted in foods prepared in some countries, but was said to be used in and exported from others.

I discussed the question of synthetic food colors with French, Belgian, German, and English representatives at the Congress. The Cancer Prevention Committee now has on file copies of regulations governing the use of synthetic dyes for foods in these countries. Photostatic copies of these documents can be supplied at cost on request. The following material in this section has been abstracted from them. Regulations applicable in the United States are contained in the United States Food and Drug Administration's Coal-Tar Color Regulations.[28] A comparative list of dyes which may be used in various countries has been published by the Society of Expert Chemists of France.[29a]

I am indebted to Prof. Dr. H. Druckrey, of Freiburg, for advice on the German position. In West Germany the use of artificial food colors is governed by the law of July 5, 1887. This law was considered to be superannuated, and the German

25. Druckrey, H.: Contributions to the Pharmacology of Carcinogenic Substances: Researches with Aniline, Arch. exper. Path. u. Pharmakol. **210**:137-158, 1950.

26. Kirby, A., and Peacock, P. R.: Liver Tumours in Mice Injected with Commercial Food Dyes, Glasgow M. J. **30**:364-372, 1949.

27. Resolution No. 11, Acta Unio internat. contra cancrum **7**:(Pt. 1):24, 1950.

28. Coal-Tar Color Regulations, U. S. Food and Drug Administration, 1940. (A copy of these regulations may be obtained from Superintendent of Documents, Washington 25, D. C., at a cost of 20c.)

29. Ruiz, I. S. L.: (*a*) Rapport sur les trauvaux de la commission constituée par la Societé des experts-chimistes de France pour une revision de la legislation concernant la coloration des denrées alimentaires, Ann. falsifications et fraudes **41**:520-528, 1948; (*b*) ibid. **42**:47-51, 1949.

Research Council appointed a commission to recommend revision. Prof. Dr. Druckrey is a member of this commission. After a search of the literature, this commission issued a report [30] listing 14 dyes which it considered adequately tested for toxicity and safe for use in foods. These dyes, together with their reference numbers in the Colour Index,[31] are:

Acid yellow (No. 16). Sodium salt of aminoazobenzene disulfonic acid with not more than 3% of the sodium salt of aminoazobenzene monosulfonic acid.

Tartrazine (No. 640). Sodium salt of 4-*p*-sulfobenzene-azo-1-*p*-sulfophenyl-5-hydroxypyrazol-3-carboxylic acid.

Quinoline yellow (No. 801). Sodium salt of quinophthalone disulfonic acid.

Chrysoin SGX (not listed in Colour Index). Disodium salt of 1-amino-benzol-2,4-disulfonic acid-azo-resorcin.

Carmoisine A (No. 179). Sodium salt of 4-sulfo-α-naphthalene-azo-α-naphthol-4-sulfonic acid.

Fast Red E (No. 182). Sodium salt of 4-sulfo-α-naphthalene-azo-β-naphthol-6-sulfonic acid.

Amaranth (No. 184). Sodium salt of 4-sulfo-α-naphthalene-azo-β-naphthol-3:6-disulfonic acid.

Cochineal Red A (No. 185). Sodium salt of 4-sulfo-α-naphthalene-azo-β-naphthol-6:8-disulfonic acid.

Ponceau 6R (No. 186). Sodium salt of 4-sulfo-α-naphthalene-azo-β-naphthol-3:6:8-trisulfonic acid.

Erythrosin, bluish (No. 773). Sodium or potassium salt of tetraiodofluorescein (for coloring of whole fruits only).

"Palatin—scharlach neu."

Alizanthrene Blue R (No. 1106). N-dihydro-1:2:1':2'-anthraquinone-azine.

Indigo carmine (No. 1180). Sodium salt of indigotin-5:5'-disulfonic acid.

"Brilliantschwarz neu."

For the French regulations, I am indebted to Prof. René Truhaut, University of Paris. Prof. Truhaut is serving on a commission of the French Academy of Medicine, which is charged with formulation of new regulations on food colors. In France, a *law* is the act of a legislative body (now the National Assembly). An *arrêté* or *décret* is an executive order promulgated by a ministry or other administrative office. Regulations setting forth coloring matters that may be used in specified foods and drinks were given in the *arrêté* of June 28, 1912, issued jointly by the ministries of agriculture, interior, commerce and industry in connection with the law of Aug. 1, 1905, for the repression of frauds and falsifications in foods. The *arrêté* just cited was concerned as much with falsification of foods as with possible toxic action of coloring matters. Therefore, the colors that could be used in certain types of foods were rigidly limited. No added color was permitted for margarine.

In 1946, the Society of Expert Chemists of France created a commission to study revision of the *arrêté* of June 28, 1912. The report of this commission [29] recommended that auramine, malachite green, and methyl violet be dropped from the list of permissible colors, citing certain references indicating a toxic action on the part of these dyes. Approval of certain other dyes was recommended. The report of this commission contains a valuable list showing the differences between regulations governing the use of artificial food colors in various countries. A

30. Resolution, Deutscher Forschungsrat, Fachkomission zur Bearbeitung des Lebensmittelfarbstoffproblems Stuttgart, 1950. (7 pp.)

31. Rowe, F. M.: Colour Index, ed. 1, London, Society of Dyers and Colourists, 1924.

second report of this commission [29b] revised the form of the list proposed in the commission's earlier report. Recognition was made of a government decree of Aug. 11, 1947 permitting the use of yellow AB and yellow OB for coloring margarine. The commission stated that these two dyes were suspect as hazardous to health by reason of the aromatic amine group in their molecules and recommended azoxy-dyes as preferable to amino-dyes such as yellow AB or OB.

In 1949, the Commission on Food and Nutrition of the Academy of Medicine published several notes relative to the use of artificial food colors.[32] This commission made a decision against using yellow AB or yellow OB in margarine. It reviewed complaints that some French food products were undersold both abroad and in France by products made in other countries and containing certain artificial colors not permitted to French manufacturers but not excluded from being imported into France in foods of foreign manufacture. Nevertheless, the commission decided against the request of French manufacturers for authorization of naphthol yellow S, indigo blue, and light green SF, yellowish. The latter dye has been claimed to cause cancer in rats.[33]

Finally an *arrêté* promulgated by the Council of State on Oct. 28, 1949, forbade the artificial coloring of margarine, noting however, that there was no objection to the use of naturally colored fats, such as palm oil, in the manufacture of margarine. This act means that the legislation now in force in France on the subject of artificial food colors is the *arrêté* of June 28, 1912, all subsequent modifications having been revoked at one time or another. Revision of these regulations is now under consideration by a commission of the French Academy of Medicine. Prof. Truhaut states that this commission has given a decision against any synthetic dyes being used in foods destined for human consumption. This decision was motivated in part by a desire to prevent frauds, in part by the view that synthetic dyes contribute nothing to nutritive values but introduce into foods a class of compounds which may be carcinogenic in themselves or may contain carcinogenic contaminants carried over from materials used in their manufacture. Naturally occurring vegetable dyes were recommended to replace synthetic dyes.

A similar resolution was adopted in Belgium at a cancer congress in 1939 [34] and has recently been resubmitted to the Belgian Ministry of Health by Dr. R. Reding, of Louvain, Belgium. Belgian food-dye regulations have been supplied to us through the courtesy of Prof. Maisin by Mlle. M.-Th. Cailie, of the Queen Elizabeth Anti-Cancer League in Brussels. Mlle. Cailie advised that the legal basis for the use of food dyes in Belgium is contained in the *arrêté royal* of Dec. 10, 1890, but that in practice the use of 23 synthetic dyes is permitted. These are listed in a document obtainable from the Service d'inspection des denrées alimentaires de l'état, 22 Place de Brouckère, Brussels. The Belgian list can be found in a publication previously cited.[29a]

From the preceding text it will be seen that the viewpoints in the several countries range from condemnation of all synthetic food dyes to approval of dyes found

32. Tanon, L.: Rapport de la Commission de l'alimentation et de la nutrition, Bull. Acad. nat. méd. **133**:337, 376 and 576, 1949.

33. Harris, P. N.: Production of Sarcoma in Rats with Light Green SF, Cancer Res. **7**:35-36, 1947.

34. Reding, R.: Des dangers de cancérisation résultant de l'emploi de colorants dans l'alimentation et en thérapeutique, Acta Unio internat. contra cancrum **4**:735-754, 1939.

harmless in properly conducted tests on animals. Although cancer has been provoked by certain dyes in animals, it could be argued that this should not prohibit their being used in human foods, since there is no evidence that man would respond to them in the same manner as animals. Conversely, it could be urged that a negative result of an animal test does not prove the harmlessness of a dye for man. Underlying these questions as to the value of animal tests in supporting decisions to permit or to prohibit any specific dye is the fact that many dyes are prepared from beta-naphthylamine, which is known to cause cancer in man. It is not known whether free beta-naphthylamine can be liberated in the human body from dyes containing it in combined form, but free beta-naphthylamine was stated to be carried over into the finished dyes to varying degrees in the process of manufacture. Another highly carcinogenic chemical used in dye manufacture is ortho-aminoazotoluene.

V. SOURCES OF STATISTICAL DATA ON OCCUPATIONAL FACTORS IN CANCER

Great Britain.—Death certificates for England and Wales are filed at the office of the Registrar-General in London. The most recent analysis was published in 1949 and contains breakdowns of cancer mortality by age, site, sex, and geographic area.[35] It thus provides base-line data on the general population, which can be used as a yardstick to judge claims that cancer of any particular site may be unusually common in some particular group of workers. The death certificates contain statements as to occupation. An extensive analysis of death-certificate data up to 1931 for cancer in relation to occupation has been made by the Chief Medical Statistician, Dr. Percy Stocks.[36] The most informative and detailed yearly account of industrial diseases in England is the "Annual Report of the Chief Inspector of Factories".[37]

Until 1937, figures pertinent to our field were published by the Scottish National Health Insurance organization, as reviewed by Padley.[38] This source has now been incorporated into the new Ministry of National Insurance. This ministry will issue annual reports through His Majesty's Stationery Office. The first report is soon to appear and will cover data of the past two years. These reports should furnish the most extensive data on morbidity, while the Registrar-General's Review will continue to afford the most complete data on mortality. The reports of the Ministry of National Insurance will provide information on occupation in relation to disease, but it is doubtful whether the system adopted for coding occupations will distinguish between office and plant personnel. The necessity for making this distinction has been emphasized by Mr. E. A. Lew, New York, who pointed out that a high incidence of cancer in plant-operating personnel exposed to a hazardous material can be diluted beyond statistical recognition when data are collected so as to include

35. The Registrar-General's Statistical Review of England and Wales for the Six Years 1940-1945, Vol. 1, Medical, London, His Majesty's Stationery Office, 1949. (This 388-page publication is priced at 6 shillings, 6 pence.)

36. Stocks, Percy: Occupational Mortality, in The Registrar-General's Decennial Supplement, London, His Majesty's Stationery Office, 1938, Pt. IIa, 400 pp.

37. Annual Report of the Chief Inspector of Factories for the Year 1948, London, His Majesty's Stationery Office, 1949. (This 158-page report is priced at 3 shillings.)

38. Padley, R.: Studies on Age and Wastage in Industrial Populations, British J. Social Med. 1:213-237, 1947.

the same industry's office workers exposed to no hazards other than typewriters and filing cabinets.[39]

Occupational data based on more specific details of the actual job may be forthcoming from a scheme described to me by Dr. J. A. H. Waterhouse, of the University of Birmingham (England), where data from hospitals in the Midlands are to be coded. The proposed forms contain items for cancer and also the following:

Industry (Code F) Specify.....years.....
Occupation Specify.....years.....
Previous occupation and industry if retired.....years.....

Code F refers to a letter code which breaks down British industries into about a hundred categories. It is the code developed and used by the Ministry of National Insurance. The additional item for "Occupation" represents an effort to obtain more specific data on the individual's actual job within the industry.

Recently, physicians have beeen required to file a card with the General Register Office for each cancer patient. These cancer records are in process of being analyzed by Dr. Percy Stocks. From the design of the cards it is apparent that their chief purpose is to provide data on matters of diagnosis, treatment, and fate. There is, however, one line designated "Occupation. . . . . " and the instructions request notation of any change in occupation in the preceding 10 years. This request has evident merit and would have more if a place to enter the answer were provided. For example, a form used in New York presents the question as follows:

Present occupation.....duties.....years employed.....
Chief previous occupation.....duties.....years employed.....

Extensive information on skin cancer exists in Britain as a result of the Workmen's Compensation Act, which recognizes the occupational nature of skin cancers due to pitch, tar, soot, bitumen, mineral oil, or paraffin and requires that these be reported. Evolution of this legislation and analyses of consequent medical findings have been reviewed by Dr. S. A. Henry in the valuable issue of the *British Medical Bulletin* devoted to chemical carcinogenesis [5a] and elsewhere [5b] The largest single group of skin tumors reported from this source derives from the cotton textile industry, as detailed in my section on shale oil. In recent years, the majority of cases have come from gas- and tar-works employees. The petroleum industry has contributed a negligible number of cases. It is interesting to note the great variety of trades in which skin tumors have been certified as of occupational origin, owing to exposure to one or more of the agents specified in the Compensation Law. Thus, 16 cases of skin cancer, in 2 of which it affected the scrotum, have been reported among optical-lens workers. The hazard for these workers has been traced to the pitch used to mount the glass for grinding.

I could discover very little information on the populations at risk in the various categories of employment to which occupational skin tumors were assigned. In occupations from which only a few cases have been reported, it is thus not possible to evaluate the significance of the alleged occupational factor on statistical grounds. Skin cancer is increasingly frequent with age, and some spontaneous skin tumors are undoubtedly included in the groups attributed to occupational factors under the

39. Lew, E. A.: Use of Life Insurance Records for Cancer Studies, A. M. A. Arch. Indust. Hyg., this issue, p. 198.

British law. In the absence of statistical criteria for certain occupations involving small groups, decisions as to the occupational nature of a tumor can sometimes be reached on other grounds. For example, Prof. J. R. Squire described to me a patient who used his bare hands in molding battery casings from hot pitch. This man's hands bore several cancers, the occupational origin of which could hardly be questioned. Similarly, an occupational causation is indicated in cancer of the scrotum, which is an uncommon site for cancer in persons not exposed to recognized carcinogenic materials.

A statistical study of cancer of the lung and of the larynx has been published by Sir Ernest and Lady Kennaway,[40] who have also reviewed publications of the General Register Office pertaining to cancer.[41] As brought out in my section on asbestos, valuable data on lung cancer have emerged through the Pneumoconiosis Board.

A statistical study of bladder tumors with reference to occupation is being conducted by Dr. R. A. M. Case and his associates at the Chester Beatty Research Institute, London. This group is inquiring into the occupational histories of bladder-tumor patients seen at various hospitals in England. Industries in the selected areas are collaborating to provide data on the populations at risk in situations where bladder tumors appear to have some connection with employment.

France.—The October, 1949, issue of the *Semaine des hôpitaux de Paris* was devoted to occupational medicine. The leading article, by Prof. René Fabre, dean of the Institute of Industrial Hygiene, University of Paris, described the development of industrial medicine and pertinent legislation in France.[42] According to recent French legislation cited by Dean Fabre, a report on diseases of occupational origin must be appended by the factory physician to the annual financial report to the company.

Prof. René Truhaut, of the University of Paris, advised that a decree of June 23, 1947, requires official notification of occupational diseases caused, among other things, by "pitch, tar, bitumen, asphalt, mineral oils, paraffins, and other substances irritant or carcinogenic for the skin." The French law in this respect is similar to the section of the British Compensation Act cited above. The notifications must be made to the Ministère du Travail. No substantial amount of information is yet available from this source. The same is true of cancer statistics being compiled under the direction of Dr. Pierre Denoix at the Ministère de Santé Publique. The French Anti-Cancer League does not have data suitable for study of occupational factors, according to the statement of its director, Dr. Huguenin. Dr. Huguenin and his associates have, however, published a study of the occupational history of 112 individuals with lung cancer. They noted that 18 were metal workers and suggested that mists of cutting oils laden with metallic dusts may have played a role.[43]

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40. Kennaway, E. L., and Kennaway, N. M.: A Further Study of the Incidence of Cancer of the Lung and Larynx, Brit. J. Cancer 1:260-298, 1947.

41. Kennaway, E. L.: The Data Relating to Cancer in the Publications of the General Register Office, Brit. J. Cancer 4:158-172, 1950.

42. Fabre, R.: L'hygiène et la toxicologie industrielles dans leur rapports avec la médecine du travail, Semaine hôp. Paris 25:3065-3073, 1949.

43. Huguenin, R.; Fauvet, J., and Mazabrand, M.: Rôle eventuel des nebulisations d'huiles industrielles dans la pathogenie des cancers bronco-pulmonaires, Arch. mal. profess. 2:48-51, 1950.

An excellent book on chemical carcinogens has been brought out by Prof. Truhaut.[44]

Holland.—Dr. J. Versluys presented a paper at the Fifth International Cancer Congress at Paris in which he stressed the need for distinguishing between occupational and social factors in evaluating an increased incidence of cancer in any particular group. For example, he found that farmers have a greater incidence of gastric cancer than males in general in Holland. However, gastric cancer was likewise more common in farmers' wives than in married women in general in Holland. Hence he concluded that the increased incidence of gastric cancer in this situation had a social rather than an occupational significance. This concept, earlier advanced by Stocks,[45] merits consideration in the planning of occupational tumor surveys. Dr. Versluys has published extensive statistical analyses of cancer deaths in Holland.[46]

Denmark.—Lung cancer appears to be more common in urban than in rural districts of Denmark, while gastric cancer occurs with equal frequency in each type of area according to data published by Clemmesen and Busk.[47] These authors considered that diagnostic facilities could account for the greater number of lung cancer cases in their urban population. Dr. Clemmesen stated that about 20% of the 4-million population of Denmark are now employed in industries. These are light industries for the most part, developed during the war, the country being traditionally devoted to dairying and agriculture. He felt that information on the type of employment was not sufficiently accurate for statistical purposes.

Other Sources.—I learned nothing of occupational tumor data that may be available in Norway and Sweden, where public health statistics are notably good. The dislocations of war make doubtful the obtaining of much data from Germany within the near future. A valuable Italian study on occupational bladder tumors has been referred to in my section on dyestuffs. Dr. Aage Grut, of the International Labor Office in Geneva, Switzerland, indicated that data on occupational cancer hazards may again be collated by that organization, which published a detailed work on this subject some years ago.[48]

At the Fifth International Cancer Congress, in Paris, I presented a paper describing experimental studies at New York University on carcinogenic petroleum derivatives [49] and a paper describing the general organization of occupational tumor investigations at the Institute of Industrial Medicine, New York University.[50] In

44. Truhaut, R.: Les facteurs chimiques de cancérisation, Biol. méd. **38**:1-47 and 89-115, 1949. (This work is available in a 77-page reprint, 21 Rue Jean-Goujon, Paris.)

45. Stocks, P.: The Effects of Occupation and of Its Accompanying Environment on Mortality, J. Roy. Statist. Soc. **101**(IV):669-706, 1938.

46. Versluys, J.: Cancer and Occupation in the Netherlands, Brit. J. Cancer **3**:161-185, 1949.

47. Clemmesen, J., and Busk, T.: Cancer Mortality Among Males and Females in Denmark, England and Switzerland, Cancer Res. **9**:411-414 and 415-421, 1949.

48. Encyclopoedia of Hygiene, Pathology and Social Welfare Studied from the Point of View of Labor, Industry and Trades, brochure edition, International Labour Office, Geneva, 1925-1934.

49. Smith, W. E.; Sunderland, D. A., and Sugiura K.: Experimental Analysis of the Carcinogenic Activity of Certain Petroleum Products, Acta Unio internat. contra cancrum **7**(Pt. 1):173, 1950. (See also footnote 6).

50. Smith, W. E.: Environmental Cancer Program at the Institute of Industrial Medicine, New York University-Bellevue Medical Center, Acta Unio internat. contra cancrum, to be published.

July, 1950, a conference was held at Oxford dealing with cancer in relation to sociological and environmental factors other than occupation. Proceedings of this conference have been published.[51]

ABSTRACT OF DISCUSSION

DR. PAUL CARTIER, L'Annonciation, Que., Canada: I have been asked to describe our experience at the Thetford Industrial Clinic in Quebec, where we see men engaged in the asbestos-mining industry in Canada. Table 3 presents data on eight cases of primary cancer of the lung which we have detected among 4,000 asbestos workers between 1940 and 1950.

In addition to those listed in the table, there was a case in which there was quite a definite clinical and radiological history of cancer of the lung but for which, unfortunately, no autopsy was performed. Also there were three other cases with a strong suspicion in favor of a cancer of the lung but for which no sufficient data are available.

On analyzing these data it seems obvious that many points would need discussion before anyone will be able to establish a causal relationship between these pathological findings and the asbestos factor.

Is it not more logical to think that the same causal factor will produce the same type of tumor, and, therefore, why do we observe such a variety of malignant tumors?

TABLE 3.—*Cases of Carcinoma of the Lungs Detected Among 4,000 Asbestos Workers 1940-1950*

Patient	Years of Exposure	Years in Industry	Age at Death	Degree of Asbestosis	Type of Tumor
J. A.	30	34	59	Minimal	Bronchogenic carcinoma
A. A.	25	25	57	Minimal	Bronchogenic carcinoma
A. L.	21	21	51	Advanced	Mediastinal lymphosarcoma with pulmonary metastasis
L. G.	11	17	54	None	Bronchogenic carcinoma
L. L.	10	26	66	Minimal	Pleural mesothelioma*
E. G.	2	14	64	None	Bronchogenic carcinoma
C. B.	None significant	27	59	....	Bronchogenic carcinoma (thoracotomy)
W. C.	None	28	65	None	Pleural mesothelioma*

* "Standard Nomenclature of Diseases and Operations" published by the American Medical Association (New York, The Blakiston Company, 1952) suggests the term "mesothelial sarcoma."

If for a moment we may assume that the asbestos fibers might produce a bronchogenic carcinoma in asbestotic employees with significant exposure, then only two cases of the series would serve as evidence because the cases of mesothelioma or lymphosarcoma and cases without exposure or without asbestosis do not have the conditions required.

As a last remark, it would appear necessary that any statistics on occupational cancer of the lung, to be conclusive, should indicate the precise variety of lung cancer.

MR. EDWARD A. LEW, New York: The difference in the frequency of lung cancer in persons with asbestotic lungs as compared with the large group of silicotics provided by the Pneumoconiosis Board seems impressive. However, one might wonder whether the two groups had been examined for cancer with equal care. I am impressed by the fact that when different groups of lungs were studied by the same observer, Dr. Gloyne, the differences in frequency of lung cancer were much less. If we restrict our attention solely to Dr. Gloyne's series, I am not sure that the differences are statistically significant.

DR. A. J. LANZA, New York: I think it is important to distinguish between cases of clinically recognizable and fatal lung cancer, on one hand, and cases in which the diagnosis of lung cancer has been made as more or less of an incidental finding at autopsy, on the other. The English claim for an association between lung cancer and asbestosis has been based, it seems to me, on data obtained from lungs that a pathologist has searched with a microscope. I wonder how many

51. Conference on Geographical Pathology and Demography of Cancer, J. Nat. Cancer Inst. **11**:627-662, 1950.

cases of lung cancer would be found if lungs from any sort of population were subjected to the same minute scrutiny?

DR. SMITH: In regard to Dr. Cartier's query as to the significance of different types of lung cancer, it may be pertinent to note that a diversity of tumors was found in the lungs of chromate workers reviewed by Dr. Anna Baetjer. Experimentally, the polycyclic hydrocarbons evoke a great variety of tumor types. If asbestos is carcinogenic, I would not expect to see it produce only one type of tumor. I am interested in your observation of two cases of pleural mesothelioma. This is a rather rare tumor. In examining pathological material sent us from England by Dr. Hinson, we found among six cancerous asbestotic lungs two presenting alveolar cell carcinoma. These tumors are often diagnosed as "pleural mesothelioma." I should very much like to exchange slides with you.

In reply to Mr. Lew and Dr. Lanza, it was my understanding that the English cases of silicosis and their cases of asbestosis were handled in the same general fashion through the Pneumoconiosis Board and that the lung cancer rate found in silicotics could therefore serve as a reasonably satisfactory control for the lung cancer rate in cases of asbestosis. In Dr. Gloyne's series of 81 cases of lung cancer in the several pneumoconiosis groups and in the control group, the tumor was evident in the gross in all except 6. Some of his material was destroyed during the bombing of London, but his recollection was that all of the cancers in asbestotics were recognizable in the gross.

DR. JOHN L. POOL, New York: Have experimental studies thrown any light on the question of lung cancer in relation to asbestosis?

DR. SMITH: In 1941, Nordmann and Sorge in Germany claimed to have produced cancer in the lungs of mice by exposing them repeatedly to asbestos dust. Their statement that cancer had resulted in 20% of their exposed animals is occasionally quoted. Actually, their "20%" figure referred only to two mice, one of which had a type of tumor that occurs commonly as a spontaneous growth in mice. The other they considered to be a squamous cell carcinoma, but their photograph does not impress me as that of epidermoid carcinoma. It seems rather to show merely an area of squamous cell metaplasia.