sions occurred in the majority of cases with less than one year's treatment and continued in 8 cases for more than two months is convincing evidence that the remission was induced rather than spontaneous. It should be remembered, however, that if treatment is continued for more than eighteen months and then discontinued, the resultant remission might well be a natural one.

It has been suggested that thiouracil could not induce a relatively long remission because it produces in the gland a hyperplastic but functionally inefficient state. It has been recognized that a hyperplastic state of the thyroid can exist in a patient experiencing a relatively permanent remission of his thyrotoxicosis. This has been demonstrated by the structure of the remnant of the thyroid gland after thyroidectomy by Rienhoff [10] and Branch. They examined sections of the thyroid gland removed several months after thyroidectomy and found the characteristic evidence of stimulation of the thyroid. Even though this state of hyperplasia persists, Preston and Thompson [11] concluded that a single thyroidectomy may accomplish control of the toxic state sufficiently to avoid subsequent operations in 85 per cent of the patients.

Treatment with thiouracil has the same effect as thyroidectomy, at least temporarily. This is accomplished by reducing the function of the thyroid tissue by interference in the iodine concentration and oxidation process of the gland. It is entirely possible that the hyperplastic state of the thyroid induced by thiouracil changes to a state of normal involution after a variable time. Evidence in support of this is to be found in the report of Shirer and Cohen,[12] who observed a normal morphologic picture in a thyroid gland removed from a patient previously treated unsuccessfully for seven months with thiouracil.

Further evidence of the active effect of thiouracil in producing a more permanent change in thyroid function is found in the case reported by Barr,[4] and in 1 observed in our series in which a thiouracil induced picture of myxedema recovered slowly over a period of six months after treatment with thiouracil was discontinued.

In our opinion this evidence indicates that thiouracil does more than iodine in that it produces a change in the thyrotoxic state which persists after the administration of the drug is discontinued.

CONCLUSIONS

Thiouracil may be used in about one third of the thyrotoxic patients only as preoperative treatment, since these patients possess nodular goiters which might develop a malignant condition. Another 7 per cent of the total number will require thyroidectomy on account of complications which occur during thiouracil therapy. The most serious of these complications to be kept in mind is agranulocytosis.[8] About 15 per cent of the patients with thyrotoxicosis will leave the physician's care for personal reasons of the patient, which are in some instances related to difficulties encountered in thiouracil therapy.

In the remaining 45 per cent of the total group, made up of those with toxic hyperplastic goiter, thiouracil therapy may be discontinued at the end of a little over an average of ten months with the prospect that 60 to 80 per cent of the patients will experience a relatively persistent drug induced remission. For this selected group, at least during the period of observation which has continued to date, this result is as satisfactory as that of subtotal thyroidectomy [illegible] patients with thyrotoxicosis, how[illegible] by surgical means. Those recei[illegible] continue treatment with the drug [illegible] For these reasons surgery is still th[illegible] in the management of this cond[illegible] superior to iodine, however, as it [illegible] its action and induces a more complete and permanent remission in patients with this disorder. In the treatment of selected cases of thyrotoxicosis, therefore, thiouracil treatment must be considered as a form of therapy which has promise, and ultimately it may prove to be as satisfactory as thyroidectomy in this group of patients.

10. Rienhoff, cited by Fitz.[8]
11. Preston, F. W., and Thompson, W. O.: Persistence and Recurrence of Toxic Goiter Following Subtotal Thyroidectomy, Arch. Int. Med. 69: 1019 (June) 1942.
12. Shirer, J. W., and Cohen, M.: The Effects of Thiouracil on the Thyroid Gland, Ann. Int. Med. 23: 790 (Nov.) 1945.

INDUSTRIAL MANAGEMENT AND OCCUPATIONAL CANCER

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The term "occupational cancer" applies to malignant tumors which originate in persons during the course of and as the result of the regular and usually prolonged exercise of certain occupational activities which entail contact with some exogenous, physical or chemical carcinogenic agent acting in proper intensity. Occupational cancers are in general elicited by specific factors which form an integral part of the ordinary working conditions and thus are not the result of some unforeseen, accidental injury sustained while at work.

Although a few of the cancers so far recognized as of occupational origin have been known or have existed without correct recognition prior to the advent of the modern industrial era, such as the soot cancer of the chimney sweeps and the cancer of the lung of the cobalt and uranium miners in Schneeberg and Joachimsthal, the great majority of occupational cancers appeared after the start of the present industrial development and as a result of it. During the last century there occurred not only a constant rise in the absolute number of these malignant growths but also a decided increase in the types of organs affected by them, in the number of exogenous occupational agents involved in their production and in the variety of manufacturing establishments in which workers were afflicted with them.

An analysis of the available data on occupational cancer has shown that the type of the resulting tumor, the length of the latent period preceding its manifestation, the organ affected and the age of the person involved depend on the character of the carcinogenic agent, the type and intensity of exposure and the age of the person when the first exposure takes place. The soot cancer of the scrotum found in chimney sweeps, for instance, was observed some hundred and twenty-five years ago even in children, since boys as young as 4 years were used in England at that time for cleaning chimneys. The exposure to the carcinogenic soot during this operation was severe, and the degree of cleanliness among these unfortunate youth was very low. When, during the middle of the last century, the English government repeatedly raised the age limit of the apprentices of this trade, there followed a gradual rise of the age range at which the scrotal cancers appeared among chimney sweeps. At the same time the institution of better hygienic conditions and the improvement of working tools and of chimney construction reduced

From the Warner Institute for Therapeutic Research.

the degree of exposure to soot. As the result of these changes the scrotal cancer of chimney sweeps in England now appears at the same age as that found in members of the general population affected by cancer of the scrotum of unknown etiology. Only the increased incidence of this particular type of tumor among chimney sweeps has remained as evidence of the action of an occupational carcinogenic agent.

However, not all occupational cancers have followed such a favorable development. Whenever the managers of new plants and their medical advisers have neglected to profit, in the construction and operation of their establishments, from the adverse experiences previously had by other manufacturers in the same fields, there has appeared some ten to fifteen years later a renewed, acute and sometimes epidemic-like occurrence of occupational cancers in these industries. Such a course of events is exemplified by the incidence of cancers of the urinary bladder in workers of the aniline dye industry. These tumors were first observed in 1895 in German dye works and were later found among the chemical workers of other countries, such as Switzerland, Italy, England, Japan and the United States. The time of appearance of cancers of the bladder of this origin followed closely the time of large scale development of chemical industries in the countries mentioned. Thus the first cancers of the bladder in chemical workers of this country were noted in 1932, that is, approximately fifteen years after the American dye industry had reached large proportions. Within the short period of six years thereafter almost 100 cases of this industrial cancer occurring in men of relative youth were placed on record from one single chemical concern, attesting to the presence of a relatively massive exposure of the workers to the causative agents—that is, betanaphthylamine and benzidine. The full significance of this incidence figure becomes apparent from the fact that there were only about 300 cases of this particular occupational cancer reported, according to the statistics of the German government, from the entire German chemical industry within a period of forty years, that is, from 1895 to 1935. Although no authentic data are available as to the occurrence and the incidence of tumors of the bladder among the workers of other American chemical concerns, the existence of such cases is known.

Cancers resulting from contact with radiant energy—that is, the rays from radioactive substances and roentgen rays, illustrate strikingly the influence which the type and intensity of contact exert on the formation of the ensuing tumor. It appears that the inhalation of radioactive gases or radioactive dust causes cancer of the lung, such as that sustained by miners in Schneeberg and Joachimsthal, whereas the local action of radioactive and roentgen energy on the skin causes the development of cancers of the skin, such as those seen in radiologists, roentgenologists, their assistants, and in x-ray tube manufacturers, physicists and engineers. The ingestion of radioactive matter, on the other hand, causes the development of cancers of the bones, such as those observed several years ago in girls who applied luminous paint to dials. However, in more recent years cancers of the blood, known as leukemias, have been noted in increasing number among physicians and radium chemists exposed frequently to relatively small doses of roentgen rays or rays from radioactive matter. These deleterious effects on the blood-forming tissue have their cancerous equivalents in the leukemias observed among persons exposed to benzene. This organic solvent, like roentgen rays and rays from radioactive substances, causes a destruction of the blood-forming tissue and results in a fatal anemia when acting in large doses, but it may elicit leukemic responses when acting in small doses and in suitable intervals on the blood-forming tissue.

In most cases of industrial cancer, experimental research on cancer has succeeded in demonstrating the specific carcinogenic agent involved by using these agents to reproduce similar tumors in animals. Definite proof of carcinogenic properties have thus been obtained for arsenic, tar, pitch, soot, crude mineral oil, crude paraffin oil, anthracene oil, shale oil, some fuel and lubricating oils, creosote, benzene, aromatic amines, ultraviolet rays, roentgen rays and rays from radioactive substances. In recent years, however, cancers of the lung have been noted among workers in chromate plants, nickel refineries and asbestos-manufacturing establishments. These tumors are either suspected or recognized as being of occupational origin. An interesting feature of these cancers is represented by the fact that the cancers of the lung in chromate workers were observed only in several German plants, while the cancers of the lung in nickel refinery workers were found exclusively in English plants where the nickel carbonyl process was used. Although the same process is employed in some nickel refineries located in Canada and the United States, cancers of the lung have not been noted among the workers employed here if full credence can be given to the meager information available on this matter. Cancer of the lung in asbestos workers, on the other hand, has been reported from Germany, England and the United States. The actual causative agent in the production of cancers of the lung in chromate, nickel and asbestos workers is still unknown.

The rapid increase in the number of recognized and suspected agents causing industrial cancers which have occurred during the last forty years makes it more likely that new and heretofore unsuspected carcinogenic agents of an industrial nature will be discovered during the coming years. Such a development is foreshadowed by observations made during recent years by American investigators. It was found that cancers of the liver developed in mice exposed to carbon tetrachloride, a commonly used organic solvent. The inhalation of ethyl carbonate (urethane), which is employed for anesthetic purposes, resulted in the appearance of cancers of the lung in mice. Tumors of the bladder were formed in rats fed diethylene glycol, which is one of the newer widely used organic solvents. Tumors of the peripheral nervous tissue were seen in the ears of rats to which crude ergot, a drug extensively used in obstetric practice, had been fed over long periods.

Occupational carcinogenic agents produce cancers in numerous organs. Cancers of the skin are elicited by contact with arsenicals, tar, pitch, soot or carbon black, crude mineral oil, lubricating oil, shale oil, crude paraffin oil, anthracene oil, solar and ultraviolet rays, roentgen rays and rays from radioactive substances. The number of industrial cancers of this organ runs into several thousands. Cancers of the nasal passages have been noted after occupational exposure to chromates, nickel carbonyl and radioactive substances. Cancers of the bronchi and lung have been traced to an industrial exposure to arsenicals, chromates, nickel carbonyl, soot, tar, asbestos and radioactive substances. Cancers of the lip have appeared following contact with tar and after prolonged exposure to solar rays, while cancers of the mouth and of the tongue seem to be etiologically related to an industrial contact with tar and arsenicals. Cancers of the bladder, of the ureter and of the kidney have fol-

lowed occupational exposures to aromatic amines such as naphthylamine, benzidine and aniline and occasionally to tar and arsenicals. Cancers of the blood, called leukemias, have resulted from contact with benzene, roentgen rays and rays from radioactive substances. The latter are also responsible for the occurrence of cancer of the bones.

The exposure time necessary for eliciting cancerous reactions in exposed workers varies greatly with the type and potency of the carcinogenic agent, with the intensity of exposure and with the susceptibility of the individual. The range is from six months to three to four decades, while the average exposure time is from five to fifteen years. In most instances occupational cancers appear in a younger age group than that found for the same cancer of unknown etiology in the general population. Age and sex factors do not, as a rule, play any role in the production of industrial cancers. The incidence rate of these tumors shows decided variations not only for the different carcinogenic agents but also for the different operations and is directly proportional to the potency of the carcinogenic agent and the intensity and length of exposure. Cancer of the bladder thus affects from 30 to 90 per cent of the severely exposed dye workers, while cancer of the lung kills from 75 to 80 per cent of the cobalt miners of the *Schneeberg mines. Carcinogenic agents eliciting* occupational cancers of the skin, on the other hand, have a lower morbidity and mortality rate because the precancerous changes of the skin preceding the appearance of the tumors gives ample warning, as a rule, of the threatening malignant condition, while the ready accessibility of the skin to therapeutic measures enhances the prognosis of cure. It is of a certain importance from an industrial point of view that the skin of colored workers is less susceptible to the cancerigenic action of solar rays and of tar, pitch and similar substances than that of white, and especially of fair-skinned, workers.

The total number of occupational cancers placed on record is small when compared with the large number of cancers of unknown etiology. It is obvious, however, that the latter group contains an undetermined number of cancers of occupational origin, as many of them either are not properly recognized or are not made a matter of public information.

Although today a great deal of evidence on the causes of occupational cancer and the conditions under which it develops is available, relatively little effort has been made to spread this knowledge among parties who are vitally concerned with this information, namely the managers and physicians of industrial concerns, although they carry the main load of controlling this preventable type of cancer. This situation is the more deplorable because the present rapid development of industry tends to extend the hazards of the known industrial carcinogenic agents while at the same time creating new ones which may cause the appearance of cancers ten to twenty years hence, unless concerted efforts are made in time to discover and control such dangers by appropriate countermeasures. It is essential that industry should devote considerably more effort than heretofore to determining the cancerous or noncancerous nature of such of its numerous products as may be suspected on general grounds of cancerigenic properties. As occupational cancers are chance experiments on cancer in man, conducted by modern industry on a large scale, which render direct, reliable and conclusive information as to the cause and mechanism of human cancer, the investigative study of these conditions deserves a great deal more consideration than it has been given in the past. The experience gained from the study of occupational cancer, and especially of its causative mechanism and its prevention and control, should prove of great value in the future in fighting cancer in general at its source; that is, it should aid in the elimination of the causes of cancer before they are capable of initiating the malignant growths. In waging this campaign it should be realized that a well planned, systematic and, probably, prolonged attack must be launched if worth while results are to be expected. However, I am convinced that with the necessary perseverance and determination this battle against occupational cancer in particular and against cancer in general can be won, if every one concerned aids in the effort.

If industry can be persuaded to finance the foundation and maintenance of an organization exclusively devoted to the study of the causation and control of industrial cancers, not only will industry be the main beneficiary of this move, but also it will greatly advance the fight against cancer in general, which is of direct concern to every one, unless it is forgotten that every tenth adult dies from this disease.

RECOMMENDATIONS FOR THE CONTROL OF OCCUPATIONAL CANCER

1. Plant management officials, industrial workers and members of the medical profession must be made increasingly aware of the fact that numerous agents of our new industrial environment possess carcinogenic properties.

2. Construction and chemical engineers should design buildings, machinery and apparatus with this hazard in mind—that is, they should try to favor the closed system of production, the installation of adequate exhaust ventilation, the use of building material which does not absorb carcinogenic substances, the avoidance of nooks, crevices and ledges where carcinogenic dust can be deposited, and the employment of wall and floor covering that can be thoroughly and repeatedly cleaned with water and steam used in connection with cleansers.

3. Adequate provision must be made for the removal of carcinogenic material from waste gases, fumes, waters, dust and the like before these waste products are released into the air, public waters or other channels affording the contact of the general population with carcinogenic industrial wastes.

4. Carcinogenic material must be packed in leakproof containers.

5. Similar appropriate protective technical measures should guard the persons handling roentgen rays and radioactive substances from being exposed to deleterious quantities of radiant energy.

6. These measures must be sufficiently extensive to protect also persons working or living in the immediate environment where physical or chemical carcinogenic agents are handled.

7. Whenever the use of carcinogenic material in industry cannot be eliminated by the use of substitutes, workers should be protected from contact with carcinogenic agents by suitable protective clothing, gloves, masks and the like and by the enforced observance of adequate hygienic measures, such as the use of washing facilities, showers and special rooms for storing street clothes and for taking meals and frequent changes of working clothes.

8. Frequent and experienced medical supervision of the workers exposed to carcinogenic material is impera-

tive for effective control of the hazard. This supervision must also extend to workers who have left the employment after having been exposed to carcinogenic agents for a sufficiently long time or who have been shifted to noncarcinogenic operations.

A nationwide survey by skilled investigators should be made to determine the actual scope of the problem of industrial cancer. Representatives of management, industrial physicians, members of the Public Health Service and of departments of industrial hygiene and possibly also representatives of the workers should participate in such a survey.

10. Precancerous and cancerous industrial diseases should be made notifiable to the departments of industrial hygiene of the various states.

11. Adequate compensation laws for occupational diseases should be passed for the protection of both management and workers against excessive awards or inadequate compensation, respectively, for claims that result from the production of occupational cancers.

12. Government inspectors should examine all industrial plants at regular intervals to determine whether or not they meet the essential safety requirements necessary for minimum protection of the workers against the hazards of industrial cancer.

13. An institute for the study of industrial cancer should be founded and should be attached to or coordinated with one of the existing large cancer research centers, in order to provide for proper integration of the results obtained by such investigations with those produced by cancer research in general. Such an organization would serve industry for consultative and investigative purposes on matters of occupational cancer.

4. A committee composed of industrial physicians, cancer research workers, industrial physicists, chemists and engineers, compensation lawyers, members of the Public Health Service and of state departments of industrial hygiene, representatives of industrial management and union officials should be created, whose members should act as a body of consultants and special experts to the Institute for the Study of Occupational Cancer.

Art and Anatomy.—Among the great artists who engaged in dissection were Michael Angelo, Raphael and Albrecht Dürer. Greatest of all was Leonardo Da Vinci (1452-1519). This gifted and versatile artist, a man centuries ahead of his time in original ideas, who visualized aviation and modern methods of warfare and who discussed many problems of engineering which were later put into practice, also made discoveries in anatomy, such as the maxillary sinus and the moderator band of the heart. He was the first to demonstrate the ventricles of the brain by wax injections and to depict correctly the fetus and its membranes within the uterus. Originally he set out to study the bones and muscles in their relation to art, but his interest grew, and he pursued his investigation of the deeper parts, the viscera, the brain, the blood vessels and especially the heart. He intended to publish a great work on anatomy in collaboration with Marco Antonio della Torre of Pavia, but this project was abandoned owing to the death of his co-worker. It is only within recent years that the value of Leonardo's contribution to anatomy has been fully appreciated. He made hundreds of sketches and manuscript s, many of which are preserved in the Royal Library at dsor and have only recently appeared in print. This apostle of naturalism in art must also be regarded as a leading pioneer in anatomy.—Guthrie, Douglas: A History of Medicine, Philadelphia, J. B. Lippincott Company, 1946.

Clinical Notes, Suggestions and New Instruments

ACUTE SYPHILITIC NEPHROSIS SUCCESSFULLY TREATED WITH PENICILLIN

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The nephrotic syndrome is defined as a clinical symptom complex characterized by profuse proteinuria, hypoalbuminemia and edema without serious renal insufficiency or hypertension. It may be seen in a variety of conditions and has been observed in connection with acute syphilis.[1]

REPORT OF CASE

History.—J. Y., a white man aged 31, was first admitted to University Hospitals July 18, 1945 with a chief complaint of generalized edema and genital ulcerations of approximately one week's duration.

In the early part of June 1945 several superficial lesions developed in the coronal sulcus of the penis. These gradually enlarged, with subsequent ulceration. July 2 he was seen by one of us (L. G. S.), who made the diagnosis of chancroid of the penis and started the patient on sulfathiazole two tablets four times daily. This was continued until July 6, when the result of the serologic test for syphilis drawn at the first interview was reported as strongly positive. On July 7 he was given 0.04 Gm. of oxophenarsine hydrochloride (Mapharsen) intravenously, with no immediate reaction. However, eight to twelve hours later he had a shaking chill and temperature elevation to 104 F. Within twelve hours the patient was again symptom free. July 10 another injection of 0.02 Gm. of oxophenarsine hydrochloride was given intravenously, without ill effect. He returned on July 15 and at that time had moderate edema of the face, legs, penis and scrotum and complained of general malaise, anorexia and low back pain. No urine examination was done at this time. On July 17, when he was seen again, the edema of the face, legs, penis and scrotum was more severe. The urinalysis revealed 4 plus proteinuria and an occasional red blood cell. On July 18 the edema was less severe and the urine contained only an occasional red blood cell. He was then referred to University Hospitals for study.

Physical Examination.—The temperature was 37 C. (98.6 F.), pulse rate 82, respiratory rate 18, blood pressure 124/72, weight 78.1 Kg. He was well developed and well nourished. He did not appear to be in distress. There were no abnormalities of the skeletal system. The mucous membranes were of normal color with no abnormal lesions. There was slight facial edema, especially noticeable about the eyes. There was no apparent edema of the upper extremities. There was moderate pitting edema of the sacrum, external genitalia, thighs and legs. The skin was normal in color and texture, with no abnormal lesions. There was a well defined, firm, freely movable nontender lymph node in the right inguinal region measuring 2 by 2 cm. There were two smaller lymph nodes similar in character in the left inguinal region. There was no other lymphadenopathy.

There was moderate periorbital edema. The conjunctivas were pale. The corneas and scleras were normal. The pupils were equal and regular, measured 4 mm. and reacted normally

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The work described in this paper was done under a contract, recommended by the committee on medical research, between the Office of Scientific Research and Development and the Western Reserve University.

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