FILE NAME: ALCOA (ALC)

DATE: 1959 Sept

DOC#: ALC085

DOCUMENT DESCRIPTION: Published Article in Medical Journal

The Ohio State Medical Journal

Published under the direction of The Council for and by the members of The Ohio State Medical Association, a scientific society, non-profit organization, with a definite membership, for scientific and educational purposes.

Vol. 55 September, 1959 No. 9

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Occupational Cancer

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Historical

OUR KNOWLEDGE of cancer of occupational origin dates from 1775. In that year, when this country was occupied with more cogent matters, Percivall Pott described in words that belonged to a more elegant generation a disease peculiar to chimney sweeps, which, as he put it, "always makes its first attack on, and its first appearance in, the inferior part of the scrotum, where . . . it pervades the skin, dartos, and membranes of the scrotum, and seizes the testicle which it inlarges, hardens, and renders truly and thoroughly distempered; from whence it makes its way up the spermatic process into the abdomen, most frequently indurating, and spoiling the inguinal glands; when arrived within the abdomen, it affects some of the viscera, and then soon becomes painfully destructive." With these words, Pott, whose name has been preserved more vividly in the orthopedic fields, described the first recorded instance of occupational cancer, of a type which in the 1920's still produced nearly 10 per cent of the cases of scrotal cancer in England.

In 1794 came the next step when Benjamin Bell observed that scrotal cancer from soot could develop in persons who were not chimney-sweeps; and in 1882, a further occupation was involved when Paris, in findings that have never been confirmed, incriminated arsenic as the cause of skin cancer in the copper smelting and tin refining industry.

In 1875, scrotal carcinoma from a different source was observed by Volkmann in Germany, who described three cases among workers engaged in separating paraffin from coal distillation, and four years later a new clinical field was entered when Härting and Hesse reported the controversial Schneeberg cancer of the lung, the symptoms of which had perhaps been described by Paracelsus 350 years previously (1531).

By the turn of the century several other occupational cancers had been described or speculated upon. Unna, in 1894, suggested that the hyperkeratotic and malignant skin lesions of sailors were due to excessive exposure to the sun, and in 1895 came the first description by Rehn of bladder cancer in the dye industry. X-ray was incriminated early in its development when Frieben described resulting skin cancer in 1906, and the effects of ionizing radiation were again recognized when Maitland found bone sarcomas in radium dial painters in 1929.

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Presented before the Section on Industrial Medicine at the Annual Meeting of the Ohio State Medical Association, Columbus April 21-24, 1959.

Still other industries began to be involved, chromates, for examples, being suggested as a cause of lung cancer by Pfeil in 1911 and confirmed by Machle years later, while in 1932 Grenfell found lung and sinus cancer in certain nickel workers, and three years later Lynch and Smith reported a high incidence in asbestos workers. Further, as a puzzling entity, Weil reported paranasal sinus cancer from isopropyl alcohol in 1952.

These are by no means all of the cancers whose origin has been attributed to occupation. Legal files are filled with allegations of cancer produced by a single trauma. It has been suggested that exposure to carbon tetrachloride in the dry cleaning industry leads to cirrhosis with a high incidence of hepatoma. Leukemia has been blamed on benzene and on x-ray exposure. Rubber has been suggested as a cause of brain tumors, etc. However, these latter suggestions would appear to have been based more on a dubiously founded theory of proximate cause, than on a critical and adequate review of the data. Nevertheless it is evident that occupational cancer exists, and before we can prevent it or protect against it, it behooves us to learn how many varieties there are, to observe where they occur, and to define the etiology as precisely as possible.

Eckhardt's recent book *Industrial Carcinogens* states that of the cancers proved to be of occupational origin, 75 per cent involve the skin, 15 per cent occur in the bladder and 10 per cent occur in lung, bone, paranasal sinuses and larynx.

Skin

Of the 75 per cent of occupational cancer involving the skin Eckhardt states that 60 per cent comes from exposure to coal tars and 36 per cent from exposure to shale oil.

Hydrocarbons: The early studies in England presented a confusing picture because scrotal cancer occurred in apparently unrelated occupational groups: Chimney-sweeps, mule spinners in cotton mills, the coal gas industry and Scottish shale pits.

To complicate the problem of correlation of these apparently unconnected occurrences numerous other factors were found to enter the picture, such as:

a. The susceptibility to the development of skin cancer appeared to vary from individual to individual;

b. The time of exposure required for its development appeared to vary from as little as four months in the case of bituminous shales to as much as 50 years in the case of British lubricating oils;

c. In some individuals the appearance of skin cancer would not manifest itself until long after exposure ceased.

As a further complication it was discovered that the carcinogenicity of these substances appeared to vary with their geographical source, the European, Middle and Far Eastern oils and tars being more carcinogenic than the American, and the Scottish shale oils being more carcinogenic than the other European.

Consequently inquiries carried out in the earlier days in Europe and the U. S. A. on the basis of the English reports showed a relatively low incidence of skin cancer from these substances. Thus, because of the interplay of many different factors it took some little time before the common factors were observed in soot, pitch, tar, mineral oil, and various petroleum tar distillates.

With the discovery by Yamagiwa and Ichikawa in Japan in 1915 that cancer could be produced in animals by prolonged inunction with coal tar, a great step forward was made; and in 1928, Twort and Ing published the results of their investigation into the carcinogenicity of various lubricating oils, showing that while sperm oils were harmless, petroleum oils possessed some carcinogenicity and Scottish shale oil was twelve times as dangerous as the petroleum oils. They also observed that the hazard of the petroleum oils varied with the boiling point of the fraction, the higher boiling series being greater than the low.

The greatest advance, however, came in the 1930's when Shear and Andervont,[10] while investigating the polycyclic hydrocarbons, discovered that the synthetic substance 1, 2, 5, 6-dibenzanthracene was carcinogenic, while Cook, Hewett, and Hieger went on to isolate from carcinogenic coal tar the related substances 3, 4-benzpyrene, and methylcholanthracene which they also showed to be carcinogenic, the former being considerably more potent than the dibenzanthracene. Kennaway, in England, went on to demonstrate that carcinogenic activity was not restricted to the polynuclear aromatic hydrocarbons but was shared by other substances such as the benzacridines, benzocarbazoles, the aminostilbenes, the aminophenyls and numerous other compounds.

The carcinogenic subclasses of polynuclear hydrocarbons can, however, be clearly related to their parent substance phenanthrene. The evidence indicates that the carcinogens so developed may combine with cellular substrates in the body and lead either directly or indirectly to the elimination of certain key proteins or enzyme-proteins essential in the regulation of normal growth.[9]

How then do we fare today in the occurrence of occupational skin cancer from oil or tars? It

is, of course, relatively more common in England and Europe than in the United States, Heller[10] showing in a study he carried out for the Rockefeller Foundation that the incidence here is rare. Cases, however, continue to occur throughout the world, the highest incidence arising in workers with cutting oils whose constituents, namely animal, vegetable, and mineral oil with added agents, vary widely accordingly to use. The active agents in cutting oils of mineral origin, nevertheless, have been shown to be the now familiar 3, 4-benzypyrene, and 9, 10-dimethyl-1, 2-benzanthracene, and consequently a degree of hazard continues to exist that warrants a continuing drive to have such oils replaced by inert materials.[8]

In the coal gas industry, which fortunately is uncommon in this country, and in the shale oil industry, nearly 4,000 cases had been reported in England by the middle of this century, and of those cases of occupational skin cancer that have occurred in this country approximately 70 per cent have been associated with the handling of gasworks tar and pitch.

In the petroleum industry, however, a greater danger arises—that from the "so-called" "slack waxes" that remain after the processing of paraffin wax, in wax or paraffin presses. These have been shown to contain some unsaturated aromatic hydrocarbons which can be highly carcinogenic, and on occasion have given rise to a clinical lesion. In addition, some of the aromatic components of high-boiling fractions of petroleum have been shown to be carcinogenic, as have some of the tars prepared from petroleum by catalytic cracking processes. Fortunately, the degree of carcinogenicity of the latter is by no means as great as that of a high temperature coal tar.

Eckhardt[20] states that 60 per cent of occupational skin cancer comes from exposure to coal tars, and 36 per cent from exposure to shale oil. Today, knowing much about the where, when and why of these occupational skin cancers, prevention is now possible.

Arsenic: We know far less about the other 4 per cent of occupational skin cancer. Arsenic was incriminated as a carcinogen in 1887 by Jonathan Hutchison whose opinion has been confirmed to a limited extent by others. Arsenic is now regarded as a cancer-auxetic, *i. e.* a substance which provokes changes in epithelial cells predisposing towards cancerous change. The occurrence of carcinoma associated with exposure to arsenic has been observed particularly in the manufacture and use of sheep dip, where a squamous cell carcinoma may be produced after many years of exposure. It has in addition been noted after prolonged medicinal treatment and has been shown in Europe to occur from the constant presence of arsenical dust on the skin. Fortunately, as with other occupational skin cancers, prompt excision is usually effective, and can be prevented by scrupulous attention to the personal hygiene of workers so exposed.

Nitrates: As far as other inorganic compounds are concerned the nitrates have been reported in Chile as a source of occupational skin cancer by Prunés[15] who describes a hyperkeratosis which after 10 to 30 years may undergo carcinomatous change. However, since only 17 cases have occurred among 30,000 workers over a 9 to 10 year period in Chile, further evaluation of this agent as a carcinogenic material is indicated.

Physical Agents: The best known physical agent implicated in carcinogenicity is ionizing radiation. The effects and dangers of radiant energy from x-ray and radioactive compounds are well known. It should be remembered that in addition to the therapeutic use of such agents, with consequent exposure of both patient and therapist, there is an increasing use of powerful radioactive sources in industry for such purposes as inspection of manufactured parts, tagging of compounds with radioactive isotopes, manufacture of luminous paints, oil surveys, etc. Thus there is an increasing risk of exposure which, if prolonged, might give rise in some cases to malignant change.

In the early days of investigation into the effects of radiation numerous instances of malignant change developed in the skin following dermatitis or ulceration, with occasionally the development of osteogenic sarcoma following exposure to ingested internal emitters in addition to the more common effects of excessive exposure. But as the hazards were slowly recognized the subsequent precautions which were devised slowly reduced the incidence of malignancy to a negligible amount. However, the danger still exists, and in the perhaps less rigidly controlled industrial situation the potential danger becomes all the greater.

Both heat and ultraviolet light have been blamed for skin cancer, but in neither instance has there ever been proof that the incidence of skin malignancy among employees with such exposure exceeds that in the general population relatively free of such exposures. Local trauma of a continuing nature, such as the rubbing of a basket or hod on a particular part certainly predisposes to or causes cancer at the site in a very limited segment of the world's population.

Bladder

The history of occupational carcinoma of the bladder dates back to the origin of the German synthetic dye industry in the latter part of the

last century, when the accidental discovery of the dye, magenta, led to the development of the vast complex that constitutes the present-day chemical industry. The condition was first observed by Rehn in 1895, who demonstrated to his skeptical colleagues the occurrence of bladder carcinoma in a series of dye workers. The causal agent he considered to be aniline, a view that was held for many years, although more recently it has been conclusively shown that pure aniline in itself is noncarcinogenic, although it may in an apparently pure state be contaminated with carcinogenic materials.

For some time after the initial discovery the reports of these tumors were confined to Germany, but with the expansion of the British synthetic dye industry during World War I cases began to appear in England in the 1920's, and by 1931 what would appear to be the first American case was reported. Despite stringent precautions in the industry, tumors continued to occur, and in 1954, Case and his colleagues in a remarkable statistical study of mortality in England and Wales during the period 1921-1950 showed that the overall risk of death from bladder carcinoma in workers engaged in the manufacture of dyestuffs was 30 times that of the general population.[5,6]

However, along with the development of the dye industry, research into the causal agent was proceeding in Germany, England and the U. S. A. and before long it was etsablished that the aromatic compounds were those responsible. Numerous compounds were incriminated, including aniline, toluidine, xylidine, benzidine, the naphthylamines, etc., but of recent years it has become accepted that although other carcinogenic agents exist in the dye industry the naphthylamines, particularly the beta isomer, are the primary culprits.

Occupational carcinoma was first attributed to the naphthylamines in 1898, but after World War I beta-naphthylamine became accepted as the cause on epidemiological grounds, some 10 years before bladder tumors were produced by it in dogs by Hueper and Wolfe. Both the alpha and beta isomers are common dye intermediates, developed during synthesis of the various dyes, and beta-naphthylamine, at least, has been shown to be carcinogenic to animals. Some controversy exists over the carcinogenic properties of the alpha isomer which can be separated in its pure state from the beta only with considerable difficulty, but it is generally believed that any resulting carcinogenicity arises from associated beta-naphthylamine which may contaminate it up to 5 per cent.

The discovery of diazotization by Griess in 1858 led to the development of the azo dyes for which new aromatic bases, including the naphthylamines were required. Benzidine, chemically related to the azo dyes, and incriminated as a cause for many years by Maguigan, is known to be carcinogenic to rats and dogs, and has been conclusively shown in the statistical study of Case and his colleagues in England to produce a high incidence of bladder tumor in man.

The azo dyes themselves, although evincing no evidence of carcinogenicity in man, have been shown experimentally to be carcinogenic to animals—o-aminoazotoluene, and 4-dimethylaminoazobenzene (butter yellow) producing liver neoplasms in rats and mice, and bladder tumors in dogs. The aniline dyestuffs, auramine and magenta do not appear to be carcinogenic per se.[18]

The tumor which develops from the aromatic compounds in man is of relatively low grade, and its development is influenced to some extent by the age at which exposure begins, there being a slightly increased susceptibility in older men. It generally develops in those susceptible some 4 to 18 years (average—16 years) after initial exposure, the required duration of the latter being approximately one year.

As far as the mode of action on the genito-urinary system is concerned, the compounds discussed above, although established carcinogens, do not appear to make their attack in the form in which they are absorbed. The action occurs within the bladder, renal pelvis, or ureter, and not via the blood stream, and appears to be affected by metabolites of the substances concerned. The effective carcinogens are probably hydroxy derivatives of the amines, to which man is highly susceptible. Since this susceptibility is not shared with the common experimental animals there is considerable difficulty in producing the tumor in the laboratory. There is some evidence that the urinary precursors of the orthy-hydroxy-amines are the glucuronic acid conjugates.[7]

Boyland[8] has linked this ortho-hydroxy theory with the metabolism of tryptophan, and has shown that one of the metabolites of tryptophan, 3-hydroxy-anthranilic acid, which is greatly increased in bladder carcinoma, is itself highly carcinogenic, and suggests that this is the active causal agent in the occupational carcinoma of the bladder.

The dye industry, however, is not the only source of carcinogenic aromatic amines. In 1954, Walpole and others[10] in England showed that the compound 4-aminodiphenyl, used in the manufacture of a rubber antioxidant, was a highly potent carcinogen, and shortly thereafter Melick[14] and his colleagues in the United States showed that a high incidence of workers where this com-

pound was made from 1935 to 1955 developed bladder carcinoma, although the rubber antioxidant produced from it does not appear to be carcinogenic. In addition, another compound, 2-acetoaminofluoride, used as a commercial insecticide has been shown to be carcinogenic.

Respiratory Tract

When considering occupational cancer of the respiratory system, which in this context includes the tract from the nose and paranasal sinuses to the alveoli, it is pertinent to observe that there has been a considerable overall increase in the incidence of lung cancer during the past 25 years. How much of this is due to improved diagnosis and greater frequency of autopsy and how much to atmospheric pollution, increased exposure to occupational carcinogens, and other as yet unknown factors can only be a matter of opinion. And, because of a paucity of experimental evidence that points conclusively to any specific compound, it has become more and more necessary in analyzing the occupational factor to rely on the results of the long-term controlled statistical study. However, much can be gained in this type of study and several compounds will be discussed that have been shown to be associated with a significantly increased incidence in cancer among those exposed to their hazards.

Chromium: Chromium compounds have long been known to produce chronic ulceration, dermatitis, and caustic effects, giving rise to the well known "chrome holes" (perforation of the nasal septum), chrome dermatitis, and chrome burns. These, however, are not followed by neoplastic change and it was originally thought that chromium had no carcinogenic properties. In 1936, however, some 25 cases of pulmonary carcinoma were recognized in Germany in men who produced chromates from chrome ores and residues, and in those who used chromates in tanning, plating and similar procedures.

Until 10 or 15 years ago there were few reports of cases outside Germany, but in 1948 Machle and his colleagues[14] published a study of incidence in the five chromate-producing companies of the United States showing that the death rate from respiratory cancer in the chromate industry was 16 times higher than expected. They further showed that the incidence of nasal irritation did not parallel the incidence of lung carcinoma and that the incidence of lung carcinoma varied from plant to plant in populations that were otherwise similar. Investigating further they concluded that the difference in incidence lay in the nature of the compounds handled and consequently suggested that the monochromates may be the compounds responsible for carcinogenesis. On the other hand, Koven et al., suggest that acid-soluble, water-insoluble compounds in chromate ore are the etiologic agents. At this time one may conclude that the specific etiologic agent is not known.

In Britain also, the incidence appeared to be negligible until 1955, when Bidstrup and Case[1] showed in a statistical study that the incidence of lung carcinoma in chromate workers in the previous six years was four times greater than expected.

As with other occupational cancers, the latent or induction period may be very prolonged, often as much as 20 to 30 years, and in some instances the tumor has appeared long after exposure ceased.

Nickel: Nickel, which is known for its tendency to produce a sensitization dermatitis, has also been incriminated as a potent carcinogen. A significantly higher incidence of respiratory carcinoma has been shown to occur in workers in the nickel industry, the carcinoma chiefly affecting the mucous membranes of the nose and air sinuses, although sometimes found as a bronchial carcinoma. Several theories have been propounded to explain the occurrence of these tumors, all of them handicapped until recently by lack of experimental confirmation. The original theory that the responsible agent was a metallic arsenide formed from associated compounds has been discarded largely because of a total absence of any other evidence of arsenical poisoning.

The favored theory relates the occurrence to the Mond process of nickel preparation in which nickel carbonyl is heated to drive off the carbon monoxide and allow the deposit of finely divided nickel. It is suggested that thereafter the nickel carbonyl, which hydrolizes in water to nickel and carbon monoxide, or finely divided elemental nickel, is inhaled and deposited at sites suitable for the production of the tumors. Although previously it has not been found possible to produce tumors in animals from nickel except by parenteral administration, this theory in 1958 found support from Hueper[11] who managed to produce adenocarcinoma in animals exposed to fine nickel dust.

Asbestos: There is no experimental evidence at this time to suggest that asbestos is carcinogenic in any form. It has been shown statistically in England, however, that there is a high incidence of lung cancer in asbestos workers known to be suffering from concurrent asbestosis, Doll in 1955 noting in a study of men who had worked 20 years or more in the asbestos industry that the incidence of lung carcinoma was 10 times that expected, while in the official statistics of the Chief Inspector of Factories and Workshops in

1955, 22 per cent of 222 men and 12 per cent of 143 women showed combined asbestosis and carcinoma.[8] The induction period appears to be very long and the tumor is highly malignant.

Although claimed by some that any tumor from asbestos is the result of simple irritation, it has been observed by Bonser, Faulds and Stewart[2] that in the exposure of both the asbestos worker and the iron ore miner, in each of which a high incidence of pulmonary carcinoma is noted, there is a common factor of silica-induced fibrosis which in each case precedes tumor formation. They suggest that in the one situation fibrous asbestos, and in the other iron oxide, modify the action of silica such that the silica acts more as a carcinogen and less as a fibrosing agent.

Dissenting voices however still refuse to accept asbestos as a carcinogen, and in a recent article Braun and Truan[4] report an epideminological study of asbestos workers in Canada, showing that the incidence compares favorably with that in other workers. It should be noted, however, that the asbestos exposed to these particular miners was obtained from chrysolite, while that associated with lung cancer is usually derived from hornblende.

Iron: As mentioned in connection with asbestos, an association has been shown between siderosis and pulmonary carcinoma, statistics from Germany and England indicating that the incidence of carcinoma in hematite or iron ore workers is approximately two and one-half times as frequent as in the general population. However, in view of the frequency of the siderosis of welders one wonders why more cases of pulmonary carcinomata are not seen in this group of workers if the foregoing reports are true.

Beryllium: Of perhaps more immediate local interest is the metal beryllium, noted for its wide complexity of toxic effect in extremely minute dosage. Although it has been known for some time that osteogenic sarcoma could be produced by injection of beryllium it has not been possible until recently to demonstrate any carcinogenic effect by experimental exposure analogous with that of normal occupational use. However, recently Vorwald[17] has shown that, under certain circumstances of prolonged inhalation, experimental animals could develop pulmonary carcinoma, and thus another hazard has been added to an already highly toxic material.

Asphalt, Coal Gas, Coke: In other fields, dust from asphalt paved roads has been incriminated as carcinogenic, and there was a suggestion 10 years or so ago from British investigators who examined the mortality statistics of pensioned gasworkers, that prolonged exposure to coal gas and coke predisposed to respiratory cancer; further studies, however, in 1956 could not confirm this, although it was suggested at the time that a change in processing of the coal gas could have altered the incidence.

An interesting situation arises, too, among workers in coal and graphite. Investigators[12] in the Welsh coal fields have shown that there is a significantly lower incidence in lung cancer in coal miners than in the general population, and that where massive fibrosis and cancer are found in the same lungs it is relatively unusual to find the two conditions in apposition to each other. This suggests that there is an antagonism between the carcinogenic process and the tuberculous process of progressive massive fibrosis.

Atmospheric Pollution: Occupational exposure to potential carcinogens is, however, only one factor in the etiology of lung cancer, and there are other fields requiring, and receiving, urgent exploration, notably that of general atmospheric pollution, and in particular, the smog pollution of Los Angeles, London, Pittsburgh, and the like. How much of the hazard so discovered will eventually be laid at the door of industry is as yet a matter of speculation.

Conclusion

Cancer of the skin, bladder, and respiratory tract under some circumstances are of occupational origin. In many instances the specific etiologic agent is known. When such is the case complete prevention is possible and must be applied.

There are many areas of confusion concerning the occupational origin of certain cancers. Litigation in the courts of law has muddied rather than clarified the waters.

We are of the opinion that there are a number of cancers of occupational origin as yet unrecognized and with advancing technology there will be others. To recognize these, it is necessary to have excellent epidemiological data on the incidence of cancers of all types, in all organs, by age and sex *in the general population* and not just per 1,000 hospital admission. Against these data the critical industrial physician must plot the incidence in specific employee groups. These data will provide the clues necessary to initiate definitive research. Scientific proof of cause should be the only basis for the approval of occupational claims and can be the only effective basis for prevention. The hiding of evidence that can justify this proof is to be condemned and perhaps should be countered with strong legal measures.

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A Retrospective Study of Lung Cancer in Women

In a controlled, retrospective investigation of 158 women with pulmonary carcinomas, the largest and the only statistically significant effects were associated with smoking history. The scale of relative risks by intensity of cigarette use was greater for epidermoid and undifferentiated carcinomas than for adenocarcinomas. For epidermoid and undifferentiated carcinomas all the relative risks, with respect to smoking history and rate of cigarette use, differed significantly from unity at the 0.1 per cent level.

The findings agree substantially with those from three other studies of lung cancer in women. The combined results of several investigations suggest that the characteristic excess lung-cancer mortality among males almost disappears when nonsmokers are studied, since male nonsmokers have only slightly higher rates than female nonsmokers.—William Haenzel, Michael B. Shimkin, M. D., and Nathan Mantel, Biometry Branch, National Cancer Institute, Bethesda, Md.: *J. Nat. Cancer Inst.*, 21: 825-842, 1958.

Surgical Management of Nontoxic Nodular Goiter Presents a Controversial Problem

We are confronted with two schools of thought in the management of nontoxic nodular goiter. (1) Thyroidectomy in all cases. (2) Selection of cases. There is general agreement that large nodular goiters should be removed because of pressure symptoms and for cosmetic reasons. It is also generally agreed that the high incidence of papillary and follicular cancer in asymptomatic nodular goiter in children under the age of 15 years demands thyroidectomy. Routine thyroidectomy in nodular goiter in adults in an endemic goiter area, however, would lead to many unnecessary operations.

Cancer of the thyroid is a relatively rare disease. Only .5% of deaths from all cancer results from cancer of the thyroid. Furthermore, in this area about 2% of the male and 6% of the female population have asymptomatic nodular goiters. These observations favor selection of cases for operation based on the appearance of a solitary nodule, a rapid lobular increase in size of a goiter, hard irregular nodules, palpable cervical lymph nodes, and any other suspicious changes in the gland.

Having diagnosed thyroid cancer, there are again two schools of thought regarding the treatment of the papillary and follicular types. (1) Routine en bloc resection. (2) Total lobectomy and removal of the involved lymph nodes with many variations depending upon the extent of the lesion. Since the standard en bloc resection is inadequate as a radical procedure of removing all local and regional lymphatics, its advocates tend to admit that its use as a routine procedure is questionable. Most thyroid surgeons, however, use it when extensive regional metastases are present and in recurrent disease.—Carl W. Eberbach, M.D., Milwaukee: *Wisconsin M. J.*, 58:209, April, 1959.

Ventricular Arrhythmias Due To Glucose

It has been shown that an intravenous infusion of glucose will produce a drop in serum potassium. This is apparently due to a shift of potassium ions from extracellular fluid to intracellular fluid when glucose is assimilated by muscle cells under influence of insulin. With the drop in serum potassium cardiac arrhythmias have been reported. Patients who are receiving digitalis may show signs of toxicity when their serum potassium is reduced.—Fred H. Priebe, M. D., Indianapolis: *J. Indiana M. A.*, 52:205, February, 1959.