# TOXICITY OF INDUSTRIAL METALS

SECOND EDITION

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reverberatory furnace, with small amounts of iron pyrites or galena. When cooled by passage through a series of brick chambers, the oxide condenses as a crude product to be purified by re-sublimation (Buchanan, 1961).

Arsenic can also be prepared from mispickel by heating in earthenware retorts and distilling off the arsenic condensed on sheet iron in the neck of the retort. It can also be obtained, free from oxide, by reducing pure $As_2O_3$ with zirconium.

## PROPERTIES

In its stable form arsenic is a steel-gray, brittle, crystalline metalloid. It exhibits allotropy, the two other forms usually distinguished being yellow and black respectively. It forms three oxides—the trioxide, $As_2O_3$ (the most abundant commercial source of arsenical compounds); the pentoxide, $As_2O_5$ (the primary material for many arsenical insecticides); and the tetroxide, $As_2O_4$. Atomic number, 18; atomic weight, 74·91; specific gravity, 5·73 (yellow allotrope 3·7, black allotrope 4·7; threshold limit value 0·5 mg. per c.m.).

## PROPERTIES OF ARSENIC TRIOXIDE (THE PRINCIPAL COMPOUND)

The crude arsenic trioxide dust obtained by sublimation during smelting of arsenic-containing ores consists of approximately 97 per cent of $As_2O_3$, its principal impurity being antimony trioxide. Pinto and McGill (1953) stated that the particle size of over 23 per cent of the dust is over 5·5μ. It is only slightly soluble in water but soluble in alkaline and acid solutions. It was stated by Schwartze (1922) that the toxicity of arsenic trioxide was inversely proportional to the particle size, the oral $L.D._{50}$ for the rat varying between 75 and 500 mg. of arsenic per kg. according to the size.

Other *inorganic compounds* of arsenic include arsenic chloride, (" butter of arsenic "), a colourless oily liquid used chiefly in the manufacture of pharmaceuticals; arsenites, arsenates and sulphur compounds. The arsenite salts in which the acid corresponds to arsenious and arsenic acids, while of the alkali salts, sodium meta-arsenate, which is readily soluble in water, is the most widely used. Of the arsenates, those of lead, calcium and magnesium are mainly used as spray insecticides, and in recent years magnesium arsenate has been found of value in the manufacture of fluorescent lamps.

The sulphur compounds, $As_2S_3$ (orpiment) and realgar ($As_2O_2$) have been largely supplanted as pigments by lead chromes, and as a depilatory realgar has been generally replaced by sodium sulphide.

Arsenical pigments—copper arsenite (Scheele's Green) and copper aceto arsenite (Schweinfurte Green) were formerly widely used as pigments in wallpaper, calico printing and as wood preservatives, but their use for these purposes is now much diminished, partly on account of the liberation of the toxic gas dimethyl arsine by the action of moulds.

Organic compounds of arsenic.—The arsphenamines—Salvarsan and Neosalvarsan—derived from diarsenobenzene, are best known for their therapeutic effects in protozoal diseases, which were first demonstrated following the discovery that atoxyl (sodium arsenilate) had this property, but they have now been largely supplanted by antibiotics.



## ESTIMATION OF ARSENIC

In estimating trace amounts of arsenic in biological or industrial material, it must be rendered soluble. Thereafter, there are several very well-known chemical tests—Reinsch, Marsh and Gutzeit—described in detail in standard works on analytical chemistry, and more concisely by Buchanan (1961).

Estimation by radioactivation was first described by Smales and Pate (1952) and adapted by Lenihan and Smith (1958). The sample to be irradiated is placed in an atomic pile, then converted into arsine, which is absorbed in a solution of mercury chloride and examined by a Geiger counter. Estimation by neutron activation analysis is described by Krishnan, S. S. *et al.* (1966).

## INDUSTRIAL USES

Arsenic is used industrially for the following purposes.

(1) In the manufacture of insecticides, weed killers and fungicides (usually in the form of potassium arsenite), and as a wood preservative.

(2) In glass manufacture as a bronzing or decolorizing addition, and in the production of opal glass and enamels, particularly in the majolica industry in Italy (Dechigi, 1936).

(3) As an addition to alloys in amounts of 0·3–0·5 per cent to increase hardening and heat resistance.

(4) In the manufacture of arsenical organic compounds for therapeutic use.

## MAXIMUM ALLOWABLE CONCENTRATION

The MAC recommended by the American Conference of Governmental Industrial Hygienists in 1962 and not since revised is as follows:

Arsenic (dust) 0·5 mg. per c.m.
Arsine 0·05 p.p.m. (0·2 mg. per c.m.).

## METABOLISM

Although arsenic is not an essential element of human metabolism, it is, owing to its wide distribution in nature, constantly taken into the human body in very small quantities, and is therefore regarded by most authorities as a normal constituent of the body.

Following the publication of a series of papers by Gautier (1899), claiming that amounts varying from 0·113 to 0·76 mg. per 100 g. were present in the normal mammary glands, thyroid gland, thymus gland, hair, skin and bones, and the denial of this claim by a Committee of the French Academy, wide controversy was aroused, particularly from the medico-legal experts, but as the result of a large series of examinations by Myers and Cornwall (1925) it appears to be generally agreed that such small amounts as those postulated by Gautier can be regarded as " normal ". According to Glaister (1931)

" traces of arsenic less than one part per 5 million parts of viscera should be ignored ".

## DISTRIBUTION AND STORAGE OF ABSORBED ARSENIC

About four-fifths of the amount of arsenic absorbed is stored and widely distributed in the tissues, including the liver, abdominal viscera, bone, skin, and particularly the hair and nails, where it may be detected many months after it has disappeared from the urine and faeces.

Determination of the rate of absorption of arsenic has been facilitated by the modern use of radioactive tracers. By exposing the hair to a flux of thermal neutrons, the arsenic is rendered radioactive, and its localization, as a fraction of length of the hair determined (Griffon and Barbaud, 1951). Arsenic was found in the hair in considerable amount in chemical workers manufacturing a solution of sodium arsenite (Hill and Faning, 1948)—108, 85 and 64 p.p.m. in 3 categories of exposed persons as compared with 13 p.p.m. in controls. Goldblatt and Goldblatt (1956) suggested that " a kind of equilibrium is reached in the hair which is independent of the amount of arsenic passing through the body as indicated by the markedly different urinary excretion ".

In a case of subacute poisoning of several weeks' duration, Heyndrickx (1955) found the greatest amount of arsenic in the proximal 5 cm. and from one-tenth to one-twentieth less in the more distal parts of the hair, a finding which he considered to suggest that the duration of the intake had been longer than the case history indicated.

The blood of normal women, according to Guthmann and Grass (1933), contains 20–100 μg. of arsenic per 100 g., and since they found a considerable increase during menstruation and the early months of pregnancy, they concluded that arsenic seems to have a direct relationship to growing tissue and cell proliferation. In women with carcinoma there was an average increase of 43 per cent over that of the intermenstrual normal value. In rats, about 80 per cent of the arsenic in the blood is concentrated in the red corpuscles.

Cows' milk contains amounts of arsenic varying between 32 and 60μg. per L. (Hove *et al.*, 1938).

## EXCRETION

Arsenic is excreted slowly, some appearing in the urine and, to a smaller extent, in the faeces within 24 hours, but a large proportion of the amount absorbed is stored in the tissues and eliminated at varying intervals of time. The normal value of urinary arsenic for persons with no known exposure has been variously calculated as 0·014 mg. per L. (Webster, 1941); 0·017 mg. of $As_2O_3$ per 100 ml. (Watrous and McCaughey, 1945); and 0·13 mg. per L. (Pinto and McGill, 1953). According to Grollman (1958) there is practically no difference in the urinary arsenic content of adults and children.

The urinary arsenic of workers exposed to arsenic may show much higher values than non-exposed persons. Pinto and McGill found levels of an average of 0·82 mg. per L. as compared with 0·13 for the controls, but stated that evidence of systemic poisoning is rare even with a level of 4–5 mg. per L., indicating that much more arsenic can go through the human body without causing illness than has been previously realized. Orestano and Abbate (1937) believe that the amount of arsenic eliminated in the urine is independent of the dose so long as this is tolerated.

With regard to lead arsenate, it appears from the investigations of Fairhall *et al.* (1938, 1941, 1943) that this compound is broken down in the body with subsequent excretion of most of the arsenic by the kidney, and according to Gerin (1957) the arsenic disappears from the urine more rapidly than the lead. Fairhall's findings indicated furthermore that in the presence of lead, arsenic is eliminated more intensively and that the arsenate radical either decreases the absorption or increases the excretion of lead while soluble arsenates decrease the lead storage.



## TOXICOLOGY

In acute poisoning arsenic is a general protoplasmic poison acting upon various ferment processes, especially the phosphatases (Oelkers, 1937), leading to diminished oxidation and tissue respiration. It has also a paralytic action on smooth muscle and thus acts as a vascular poison, leading to haemorrhage (Nonnenbruch *et al.*, 1936). In the cell, the toxic effect is exerted on the chromosomes, particularly—according to Bucher (1940)—as a blockage of the mitotic metaphase, a property which it shares with colchicum. It is believed by some authorities that the immediate effects on the gastro-intestinal mucous membrane are due to increased permeability of the capillaries.

In industry, acute poisoning from solid arsenic is rare; subacute and chronic poisoning usually arises from exposure to arsenic-containing dust and fume. The most dangerous arsenical compound, not used as such but occurring as the result of accident, is arsine, or hydrogen arsenite, a powerful haemolytic agent.

## ARSENICAL POISONING IN ANIMALS

Acute.—A wide variation of toxicity has been reported in various animal species and even in strains of the same species; both the particle size and the amount of impurity have been found to influence the $L.D._{50}$ dose. From the investigations of Harrison *et al.* (1958) it appears that the strain variation is less marked in the mouse than in other animals. They also found that solutions of arsenic trioxide are many times more toxic than the dry powder, and that the high purity compound was less irritant to the gastro-intestinal tract than the crude sample, possibly on account of the presence of impurities such as antimony. Gastro-intestinal damage, as evidenced by severe convulsions and retching, and haemorrhage of the stomach and intestines was a marked feature of the crude arsenic trioxide, while the pure preparation caused much less discomfort and only slight reddening of the gastric mucosa. The ultimate $L.D._{100}$, however, was less for the pure than the crude preparation (39·4 mg. of arsenic per kg. as compared with 42·9). In the liver, fatty degeneration, cell necrosis and reparative changes following acute injury by arsenic have been observed (Rössing, 1941).

Arsenic trichloride ($AsCl_3$) a liquid evaporating with emission of dense white fumes, causes a severe conjunctival reaction with chemosis and necrotic corneal lesions (Uhde, 1946).

(c) *Arsine.* In a case reported by Dernehl, Stead and Nau (1944), intense irritation of the eyes, with palpebral oedema, occurred in a metal refinery where fume was accidentally generated. Arsine was thought to be the most active agent but stibine and sulphur hydrides were also present.

(d) *Organic Arsenicals.* The extreme toxicity to the eyes of some trivalent organic compounds is due, according to Duke Elder (1954) to their rapid linkage with the sulphydryl groups in proteins and enzymes essential for carbohydrate metabolism, a view also held by Dixon and Needham (1946). The most virulent is Lewisite (chlorovinyldichloroarsine), once intended but not used for chemical warfare.

Chronic.—The chronic symptoms observed in workers exposed to arsenic and its compounds are related chiefly to the skin, mucous membranes, gastro-intestinal and nervous systems, and in a few cases disorders of the circulatory system and the liver have been recorded. German observers have described many of these manifestations from the use of arsenic as an insecticide, particularly in wine dressers (Dorle and Ziegler, 1930; Schorndorff, 1938; von Pein, 1940; von Pein and Daurhenn, 1943) though it has been suggested that the arsenic poisoning of wine dressers is not due so much to inhalation or skin contact, but as the result of ingestion of contaminated wine.

The question of a potential carcinogenic action of arsenic on organs other than the skin has been much debated. The recorded cases of carcinoma of the lung, larynx, viscera, and multiple tumours of the skin or viscera, or both, associated with chronic absorption of arsenic are strongly suggestive of such a relationship, but some "adjuvant factor" in the metabolism or hormone balance of the sufferer or in the susceptibility of the affected tissues appears to be also concerned.

## SYMPTOMS OF CHRONIC INDUSTRIAL POISONING

### SKIN LESIONS

Lesions of the skin in association with industrial exposure to arsenic were described as long ago as 1728 by Henckel (the so-called Hütten-Krätze). During the nineteenth century many cases of erythematous, pustular, or even ulcerative or gangrenous lesions were described, chiefly from the manufacture or use of Schweinfurter Green but also of other arsenical materials.

Vigne (1930), describing the cutaneous lesions occurring during the manufacture of insecticides, considered that the most hazardous compounds in this respect were arsenic trioxide and Paris Green; sodium arsenite, however, has also been found potent in producing skin lesions of very varied character. Leoncini (1933) described ulceration of the hands and feet, scrotum and perineum from its use as a vermin killer, and Tamponi (1935) reported erythema, papules and ulcerations from its use as an insecticide.

The inorganic arsenical compounds have been regarded by the majority of observers as primary cutaneous irritants, not sensitizers. Schwartz *et al.* (1947) classified arsenic disulphide, sodium arsenate and arsenite and potassium arsenate as primary irritants, but also designated arsenical compounds in general as "the principal sensitizers met with in industry". Holmquist (1951), while unable to express an opinion on the sensitizing capacity of every individual inorganic arsenical compound, found that the trioxide and pentoxide were definitely able to produce sensitivity; he considered that this capacity was shared to a large extent by other compounds of arsenic, the sensitization being dependent to some degree on the intensity of the exposure.

The question as to whether inorganic arsenical compounds can produce sensitivity to organic compounds has been discussed by Jones (1940). On the basis of two cases—workers in an arsenic mine, who showed skin reactions 11 years later following an injection of neoarsphenamine—Jones suggested that previous industrial poisoning may provide the mechanism for later sensitization to organic arsenicals.

Nature of the skin lesions.—*Acute and subacute dermatitis* is more common than the chronic or subchronic types. In the initial stages, which may arise in less than a week or only after years of employment, erythema, associated with burning and itching, is sometimes most intense around the follicles, giving the skin a spotted appearance; when occurring on the face, accompanied by swelling, this may disappear without further development or may be followed by *papular and vesicular eruptions.*

Pustular folliculitis may be accompanied by marked serous discharge, especially in areas exposed to rubbing or chafing, resulting in the formation of crusts. In some cases these lesions heal within a week leaving only slight pigmentation and desquamation; in others the skin becomes lichenified and liable to form new foci of inflammation even after cessation of exposure.

In the cases described in great detail by Holmquist (1951) where the exposure was related to the metallurgical working of copper ore in smelting works in Sweden, the dermatitis was mainly localized to the areas of greatest exposure—the face, neck, forearms, wrists and hands. It also occurred on the scrotum and thighs, the upper part of the chest and back and the lower legs. Recurrences in employees removed to departments with a lesser risk of exposure to arsenic suggested that some of the lesions were due to sensitization; this was supported by the results of patch tests, in which eczematous reactions were produced by arsenical compounds.

A less acute but very prominent feature of skin lesions due to arsenic is *hyperkeratosis*, often accompanied by hyperhidrosis, especially of the palms and soles. Under the name hyperkeratosis, Watrous and McCaughey (1945) included cracking skin, thickness and dryness of skin, and warts. A diffuse branny desquamation of the skin of the trunk and extremities with dark, deeply pigmented areas has also been described (Heyman *et al.*, 1956) and has been likened to that of Addison's disease.

A case of *arsenical melanosis* in a glass worker who also suffered from silicosis was described by Gilje (1951). In some areas the pigmentation alternated with depigmentation ("rain-drop" pigmentation); in others, especially the hands and feet, it showed a striped appearance. It was assumed that the inhaled silica-containing dust also contained arsenic. The

nature and causation of the melanosis has been investigated by several observers dating from Wyss (1890) and Gaus (1915) onwards.

Osborne (1925), summarizing his own findings and comparing them with those of the earlier observers, with whom he agreed on the whole, concluded that the pigment contained no arsenic but lipoids and melanin derived from cell metabolism, not from the " products of brokendown blood ", and that it arose chiefly in the corium and to a lesser extent in the epidermis, by an indirect action of arsenic on the mother substance of melanin.

Buchanan (1961) remarks that melanosis is certainly an indication of systemic absorption of arsenic, generally over a lengthy period, and not the result of local action.

The nails.—The presence of white striae in the fingernails, described by Mees (1919) has come to be regarded as almost a diagnostic accompaniment of arsenical polyneuritis. Mees observed this broad white band on all the fingernails of 3 cases of attempted murder or suicide by arsenic and stated that its presence in association with polyneuritis was confirmatory of the diagnosis of arsenical poisoning; it was still distinct long after the disappearance of arsenic from the urine. In the cases of Heyman *et al.* (1956), all of those who had had symptoms of arsenical intoxication for 6 weeks or more, showed this phenomenon; it was not present in 4 patients observed for less than that time. These authorities believe that an approximate estimation of the exposure to arsenic could be made from the distance of the lines from the base of the nail; but there was no evidence that the actual growth of the nail was retarded by arsenical neuropathy. In 1 patient the time of migration of the lines to the free edge of the nail was 5 months (the approximate time for the nail to grow from the matrix to the free edge in normal persons). Nevertheless, examination of 2 other patients with Mees' lines showed no arsenic in the hair or urine, indicating that these bands are not pathognomonic of arsenical intoxication.

Cancer of the skin.—The association of arsenic with skin cancer was reported by Hutchinson (1887), in relation to the internal administration of arsenic over long periods, and has been confirmed by many authorities since that time, especially from Fowler's solution (Arhelger and Kremen, 1951) and other arsenical medicinal preparations (Sommers and McManus, 1953). Skin cancer from external contact with arsenic-containing substances in industry has been relatively rarely reported; Leitch and Kennaway (1922), though they had succeeded in producing a typical squamous-cell carcinoma in animals by the external application of potassium arsenite in alcohol, stated that only two instances were on record up to that time which could reasonably be attributed to employment with arsenic ; both were workmen dealing with sheep dip.

In the series of cases of skin cancer recorded by Sommers and McManus (1953), most were associated with the medicinal use of arsenic; only 2 were occupational in origin. One of these had used lead arsenate during his work as an electroplater and had shown multiple keratoses of the hands for 5 years before biopsies of a lesion of the thumb showed hyperkeratosis and epithelial hyperplasia. Following amputation an invasive epidermoid carcinoma was found to be present.



Neubauer (1947) collected 143 published cases of arsenical epithelioma following medication with arsenic for diseases of the skin (psoriasis was predominant) and other conditions. The most common form was again Fowler's solution (potassium arsenite 1 per cent calculated as $As_2O_3$). Arsenic trioxide was also given as pills; Donovan's solution was a combination of the iodides of arsenic and mercury.

Nature of the carcinomatous lesions.—Among the varying types of arsenical cancer of the skin, epithelioma developing on the site of keratoses (the " Hutchinson type ") is the commonest. The keratotic lesions may have existed for many years before they begin to undergo malignant change to epithelioma, usually of the squamous type. Such lesions have also been recorded as developing in patches of psoriasis, and even in normal skin. The association of arsenic with multiple epitheliomatoses, sometimes of basal-cell type and of a low-grade malignancy, and with a chronic " precancerous dermatitis " (Bowen's disease), described by Bowen in 1912, is still under discussion by dermatologists.

## MUCOUS MEMBRANES

Dermatitis of the face and eyelids is sometimes accompanied by conjunctivitis, with redness, swelling and pain. Two cases of severe keratoconjunctivitis were described by Paufique and Bonamour (1946) following exposure to calcium arsenate as an insecticide. In one case corneal anaesthesia was accompanied by a corneal ulcer. There may also be irritation of the nose and pharynx, causing acute or chronic rhinitis, and of the bronchial passages.

Perforation of the nasal septum was described by Davis (1917) and by Dunlap (1921) in workers employed in copper smelting. The actual perforation is in most cases preceded by slight epistaxis, some irritation of the nose, and the formation of crusts owing to the resultant obstruction to nasal breathing, pharyngitis and possibly low-grade laryngitis. The perforation develops from a white slightly elevated area about 5 mm. in diameter followed by necrosis on both sides of the septum, when the cartilage disappears from dystrophy. It was suggested by Dunlap that the arsenic-containing dust breathed into the nose and coming into contact with the moist membrane forms arsenious acid, which causes necrosis of the septal mucosa, and by Pinto and McGill (1953) who observed similar cases in their workers exposed to arsenic trioxide, that the large particles (over 5·5 $\mu$) which form a substantial part of the dust, readily impinge on the septum.

## GASTRO-INTESTINAL DISTURBANCE

True gastro-enteritis is not a common occurrence in industrial chronic arsenical poisoning. Pinto and McGill (1953) found only one case among their workers with arsenic trioxide, but digestive disturbance, as shown by nausea and vomiting, is occasionally reported. A case described by Mayers (1954) in which severe gastro-intestinal symptoms were predominant was unusual in that it apparently remained undiagnosed for more than 20 years in spite of numerous admissions to hospital for disorders suggestive of

arsenical poisoning. The man's exposure to arsenic in the form of Paris Green powder had been heavy and included the possibility of inhalation, ingestion, and skin absorption. The gastro-intestinal disturbance began soon after he started work, with acute colic and haematemesis. He was found to have a penetrating gastric ulcer which healed but returned when he resumed work and disappeared only when exposure ceased entirely. During his 20 years of more or less intermittent exposure he had repeated attacks of exfoliative dermatitis; these also disappeared when exposure ceased but left permanent trophic skin changes with discoloration. Other symptoms characteristic of arsenical poisoning were also present—conjunctivitis, upper respiratory irritation and polyneuritis—and death was finally due to cardiovascular degeneration.

## PERIPHERAL NEURITIS

The symptoms of peripheral neuritis following exposure to arsenical compounds in industry, though infrequent, are identical with those recorded as due to ingestion (Kelynack *et al.*, 1900) and others. Unlike the peripheral neuritis of lead poisoning, in which pain and disturbance of sensibility are usually absent, arsenical polyneuritis is accompanied by pain, with burning and tenderness in the affected limbs, and difficulty in walking. These symptoms were present in the cases described by Heyman *et al.* (1956), 7 of which were said to be due to direct contact with arsenate sprays or dusts. Some of the cases had an initial stage in which the symptoms were those of acute poisoning—nausea, vomiting and diarrhoea—but in the 7 industrial workers the onset was gradual, with development of sensory disturbances in the extremities—numbness, tingling and " pins and needles "—followed by severe symmetrical weakness in the feet and legs. As in the cases described by Hassin (1930), high levels of arsenic were found in the hair and also in the urine—2·5 mg. per 100 g. in the hair, and 0·1–6 mg. in a 24-hour specimen of urine. In Hassin's cases, where the source of the arsenical poisoning was not determined, the diagnosis was confirmed also by the presence of " Mees' lines " on the nails.

The difficulty in distinguishing between the polyneuritis of lead poisoning and that of arsenic is emphasized by a case recorded by Barbier *et al.* (1942). The polyneuritic symptoms were at first diagnosed as due to lead poisoning, since the man had used lead arsenate as an insecticide spray. The outstanding feature of this case was motor weakness of the hands and difficulty in walking; the diagnosis of arsenical polyneuritis rested chiefly on the evidence of an initial gastro-intestinal disturbance and the presence of Mees' bands on the nails; there was no hyperkeratosis and no tingling or numbness of the hands and feet.

## THE LIVER

Involvement of the liver, with jaundice, sometimes ascites, was noted in early observations as a sequela of arsenical medication. Hutchinson (1887), for example, described liver injury resembling cirrhosis following arsenical treatment of chronic eczema. One of the first records of cirrhosis from the industrial use of arsenic was that of Dorle and Ziegler (1930) in wine dressers,



though, as already remarked, as in that of many successive observations on wine dressers in Germany, the ingestion of arsenic-contaminated wine is now believed to play a more important part than the actual exposure to the arsenical insecticides. Hurren and Heinlein (1943) stated that the increase in liver injury among employees in the wine industry since the introduction of arsenic spraying was to be largely attributed to the effect of arsenic, and that this injury was degenerative in character, reparable in some cases, but leading finally to cirrhosis. On the basis of the Takata-Ara reaction they found that 70 per cent of the workers examined showed a variable degree of liver injury though only 36 per cent showed a definite cirrhosis. In a fatal case with ascites a special feature was the presence of discrete parenchymal necrosis with reparative connective tissue formation. They conceded, however, that the influence of ingested alcohol could not be entirely excluded. This reservation applies also to the supplemental toxic action of nicotine, phosphorus and metabolic disturbance in similar observations by German authorities in the early years of this century.

## DISORDERS OF THE HEART AND CIRCULATION

The subjective and clinical evidence for a primary cardiac injury in arsenic workers is not very definite, but the electrocardiograph has revealed abnormalities similar to those observed in animals fed on subtoxic amounts of arsenic (Butzengeiger, 1940 and 1949; Hadjoloff, 1940 and 1957).

Among 216 wine dressers using arsenical insecticides, Butzengeiger found 55, who showed other symptoms of chronic arsenical poisoning, to have an abnormal electrocardiogram indicating a toxic myocardial effect. Among these were 36 whose myocardial injury was severe, and some of them were suffering also from peripheral disturbances indicative of endo-angiitis—gangrene of the extremities, atrophic acrodermatitis and other less severe symptoms of peripheral damage. Butzengeiger described the endo-angiitis as indistinguishable from severe arteriosclerosis or endo-angiitis obliterans.

## THE CARCINOGENIC ACTION OF ARSENIC

Examples of cancer of the skin in patients receiving arsenical medication and in arsenic workers having external contact with arsenical compounds have already been described, and there seems little doubt that carcinomas of the skin do arise especially on the sites of arsenical keratosis. The evidence for arsenical cancer of other organs is not so universally accepted, especially with regard to occupational exposure.

The view formerly held that the high incidence of lung cancer among the miners of Schneeberg and Joachimstal were due to arsenic has been more or less discarded in favour of radioactivity as the carcinogenic agent, partly because of the absence of characteristic arsenical skin changes. Hueper (1942) stated that " the possibility of a causal relation between the inhalation of arsenic dust and the development of pulmonary malignancy may be conceded but the probability of its relationship is small ".

In a clinical and experimental study by Perry *et al.* (1948) among workers

in a factory manufacturing a solution of sodium arsenate, despite the previous finding by Hill and Faning (1948) in the same factory that on a statistical basis there was a greater tendency for arsenic workers to die of cancer than for other groups, radiographic examination did not reveal any case of bronchogenic carcinoma. More recent investigations by Roth (1956, 1957) and Braun (1958) do, however, show a definitely higher incidence among wine dressers in Germany. Roth found 10 cases of bronchial carcinoma among 30 workers with arsenical skin lesions. Braun, comparing the incidence of bronchial cancer in those suffering from arsenical dermatoses during the years 1951–1957 with that between 1939 and 1952 found a greatly increased incidence in the later years. Out of 16 of an average age of 52 years, all showing keratosis and some also melanosis, pre-malignant or malignant skin changes, 9 had inoperable bronchial carcinoma.

Tumours of other organs, most frequently in association with arsenical cancers of the skin, have also been described, notably by Sommers and McManus (1953) in their review of 18 cases of visceral cancer reported in various countries up to that year. Among these, of which only 5 were industrial workers, there were 7 cases of pulmonary tumour, 3 of the mouth and tongue, 3 of the ureter and bladder, 2 of the breast, 2 of the oesophagus, 1 of the stomach and 1 of the cervix uteri. Only 6 of these had associated cancer of the skin. In their own series of 27 cases, of which only 2 were occupational, many had not only multiple skin cancers, but also, among 6 who were submitted to autopsy, 4 had separate internal cancers of the bladder, prostate, oesophagus, colon, kidney and chest wall; in 3 cases the growths were multiple.

Roth (1956) also noted 5 cases of malignant liver tumour and one of oesophageal cancer associated with liver cirrhosis, and in Braun's series there was 1 case of carcinoma of the bile ducts also associated with cirrhosis of the liver, and 1 of a suspected sarcoma of the cervical lymph glands. Rosset (1958) has recorded a case of multiple internal carcinomas in a man who more than 20 years previously had used lead arsenate to spray potatoes, and had at that time developed keratotic lesions on the palms of his hands. The latent period of development of malignant tumours of possible arsenical origin is long—13–50 years according to Sommers and McManus (1953), 13–22 years in the experience of Roth (1956) and Braun (1958).

The most disputed point in the problem of the potential carcinogenicity of arsenic appears to be whether it is a direct agent, or whether it is dependent on other factors such as tissue susceptibility, skin sensitivity, photosensitivity, or other external or internal metabolic effects. On this point it does not seem possible at present to arrive at a direct conclusion. Even Goldblatt and Goldblatt (1956) in their admirable review of industrial carcinogenesis, and with their extremely wide experience of the subject, can only say that " the arsenical compound which produces no tumour in a workman is not a carcinogen for him until he, in a given tissue, brings about a meeting between a cell in the appropriate state and the compound in a sufficient concentration . . . *and* . . . from the very few cases of occupational arsenical cancer hitherto reported it may be considered that a combination of appropriate state and sufficient concentration is rare ".



## ARSINE

Arsine (arseniuretted hydrogen; hydrogen arsenide; $AsH_3$) is not an industrial product in the economic sense, but an accidental evolution whenever nascent hydrogen is liberated in the proximity of trivalent arsenic.

## PROPERTIES

Arsine is a colourless inflammable gas with a slight garlic-like odour, depositing arsenic on exposure to light and moisture (threshold limit value for an 8-hour working day, 0·05 p.p.m.). Concentrations of 3–10 p.p.m. will produce slight symptoms after several hours' exposure and 16–30 p.p.m. are dangerous according to Doig (1958).

## OCCURRENCE

Since arsenic is present as a contaminant of many ores—zinc, lead, copper, antimony, gold, silver and tin—the formation of arsine occurs most frequently in the metallurgic industry, particularly from the action of acid on arsenic-bearing metal. It may also occur where the hydrogen ion is formed by hydrolysis, as in the reaction of moisture with calcium arsenide present as an impurity in ferrosilicon (Hake, 1910); in the process of wetting of aluminium and phosphate dross (Nau, 1948; Spolyar and Harger, 1950); in lead refining (Wills, 1948; Banik, 1956); and in the purification of tin (Macaulay and Stanley, 1956). In this last process reports from those of Legge (1924) onwards had previously recorded 30 cases of arsine poisoning with 12 deaths. Its occurrence has also been described during cyanide extraction of gold (Bulmer *et al.*, 1940); in the process of leaching of zinc (McKinstry and Hickes, 1957); very frequently in the cleaning out of furnaces and tanks (Wills, 1948; Hamilton and Hardy, 1949; Troisi, 1950); and even from mishandling of arsenical insecticides (Mohacek and Stajduhar, 1951).

## TOXICOLOGY

The fatal effects of arsine were first reported in 1815, when Gehlen, a chemist, died from inhaling it in his laboratory. It is a powerful haemolytic poison with both acute and also chronic exposure. In the acute form the mortality rate is high. Muehlberger *et al.* (1928) stated that 20 per cent of 215 cases of poisoning occurring since 1815 had been fatal; Spolyar and Harger (1950) estimated a mortality of 12 among 30 cases recorded between 1923 and 1941, while during the years 1945–1946, 13 cases, 4 of them fatal—a mortality of 31 per cent—were recorded in the Annual Reports of the Chief Inspector of Factories.

### ACUTE POISONING

The outstanding initial features of acute arsine poisoning are malaise, abdominal cramps, nausea and vomiting, and a red staining of the conjunctiva; this pigmentation, according to Macaulay and Stanley (1956), is not