ABSTRACTS

INDUSTRIAL TOXICOLOGY


An account is given of 3 patients suffering from acute and 1 from chronic lead poisoning who were treated with sodium citrate. The 3 patients with acute disease suffered from abdominal pain and diarrhoea, and in one instance jaundice. The patient with the chronic disease had complained of abdominal pain and weakness over a period of 2 years. The patients were treated with sodium citrate in doses of 1 g. four times daily for a week, at the end of which time their symptoms were relieved. In one case the renal excretion of lead was suppressed, and in 3 cases there were prolonged urinary lead concentration and a slow rise of haemoglobin to normal levels, which the authors considered was evidence of the persistence of abnormal amounts of lead in these patients; in the other case there was evidence that sodium citrate therapy hastened the excretion of lead.

The authors conclude that adequate oral doses of sodium citrate will control the symptoms of lead poisoning; they do not agree that sodium citrate increases lead excretion. Increased coproporphyrinuria was found in all 4 cases, and to explain this the authors suggest that lead may act as a block between protoporphyrin and iron and prevent their normal combination in the formation of haemoglobin. It is possible that the neuritic pain, headache, encephalopathy, and colic present in plumblism may be explained by the coproporphyrins deposited in the tissues. It is possible that the finding of coproporphyrinuria may be a valuable aid in the prevention and early diagnosis of lead poisoning.

K. M. A. Perry.


The authors describe a series of 10 patients who suffered from a syndrome of acute abdominal pain of a colicky type associated with jaundice and sudden onset of unilateral or bilateral paralysis of the upper limbs. Patients with slight paralysis showed the typical radial palsy with the escape of the supinator, but when the paralysis was severe then all the upper limb muscles were involved, and in 2 cases the lower limbs were also affected. All the patients were employed, or spent a great deal of time, in public houses or cafes, and the condition was caused by lead poisoning due to drinking mineral water with a high lead content. The differential diagnosis, clinical features, and pathology of the condition are discussed. Treatment includes the administration of Vitamins C and D and measures such as calcium injections and a diet rich in calcium to immobilize the lead, as its elimination is almost impossible.

René Mendez.


Haemorrhage from the bladder and bladder tumours caused by occupational factors in the dye industry were first described by Rehn in 1895. Since then a considerable literature has accumulated, though, curiously enough, reports in this field from France have been few, despite the flourishing dye industry in that country. Some arsenic compounds were first under suspicion, but more recent views suggest that the anilines are associated with tumour formation; also many other substances such as toluidine, xyline, various naphthalines, Congo red, and fuchsine. The aetiological significance of many of these materials is still disputed, and confusion has been caused by the discovery that many dyestuffs are not pure substances but mixtures. Thus it is said that α-naphthylamine may contain from 5 to 10% of the beta product, which is the more harmful. Though some amino compounds are admittedly dangerous others are not; this radical cannot therefore be considered by itself.

It has been suggested that bladder disorders of the type described in man are essentially due to basic aromatic and primary amines. European workers all admit the harmful properties of β-naphthylamine and benzidine, though it is not universally accepted that similar properties are possessed by aniline and α-naphthylamine.

Recent experience of the Basle clinics suggest that not only amines, but also hydrocarbons such as anthracene, are harmful. It is known that tar and its derivatives may be carcinogenic, especially to the skin, but the literature contains isolated examples of other cancers from this cause, including those of the bladder. The prolonged inhalation of anthracene fumes, as occurred in the author’s case, is rare. Though some absorption of the various carcinogenic substances may occur by other routes, the most important one is that through the lungs, by which both dust and fumes may
penetrate the body. It is known that the carcinogenic anthracene substances are eliminated through the urinary tract, and this is also the case with the amines mentioned. In many of the older factories considerable amounts of dyestuff escaped to the air as a fine dust, to which the workers were unavoidably exposed. Though the basic amino substances do no harm to the general body tissues, this appears to be due to their alteration in the tissues into harmless substances. Goldblatt regards the base itself as harmful, since such cancers are unknown in those handling phenol, acyl, or aryl derivatives of amines.

Apparently the noxious substances act on the mucosa of the urinary tract after excretion, and it is strange that no similar injuries occur in the lungs or alimentary tract. In man, who walks erect, most lesions are at the base of the bladder, while in experimental animals, as their gait would suggest, lesions tend to appear on the anterior wall of the organ. The lower incidence of lesions in the upper urinary tract is probably due to the more rapid passage of the irritant. Urinary stasis is also a factor, for as the pH rises the solubility of the amino bases falls. Some of these will come out of solution and be deposited on the floor of the bladder. Action through the blood stream in the urinary organs is also likely at times, so that the latter are exposed to double attack. Certain authors suggest that the first lesions are sub-epithelial, usually consisting in the development of new vessels. It is pointed out that, where tumours generally form, the vascular network round the bladder is richest. Circumscribed telangiectases and submucous suffusions are certainly seen in the early or pre-cancerous stages.

Many experienced workers dispute the haematogenous origin of the tumours. Whichever theory is accepted, the development of tumours many years after exposure to the irritant ceases is not easily explained. In animal experiments traces of certain dyes have been found in the bladder years after their administration.

Statistical proof of the frequency of these lesions in dye workers is not easily obtained, but it is certain that greater manufacturing precautions have diminished their incidence. In the Basle district death from this disease does not occur much earlier in dye workers than in its other victims. The author finds the average period of exposure before lesions develop to be just under 12 years, in a range between 36 and 6 years. Cancer is rare in those with acute poisoning. Acute poisoning may cause extensive but transient irritative lesions which rarely pass into a chronic stage of inflammation. Haemorrhage is an early symptom of cancerous change, but, though this was previously denied, tumours may form without the discovery of occult blood in the urine. Dysuria is common, but many symptoms are often absent until the neck of the bladder is involved or ulceration and incrustation have developed. During the latent period which is common to all tumours no symptoms at all may occur.

Diagnosis rests on early cystoscopy, an examination which should never be omitted. It may be very difficult to find the smaller tumours. Instillation of adrenaline will check bleeding and thus facilitate investigation. Diagnostic partial excision may stimulate spread. There is some suggestion that a familial tendency to carcinoma is indicated in certain cases. Benign tumours account for about a quarter of those seen in the dye industry, but these may develop cancerous changes. Simon maintains that aniline tumours have a more favourable clinical course than those of unknown aetiology. In Basle multiple primary tumours of the bladder were recorded in 10 cases, and in some of these cases other organs were affected and other types of cancer occurred.

The Basle school employs conventional treatment of the disease and recommends drastic measures to lessen exposure to the noxious agents. Prophylaxis is incomplete if regular examination of the workers is neglected; this should include cystoscopy.


Beryllium poisoning appears in acute, subacute, and chronic forms. In the first there may be contact dermatitis, conjunctivitis, or respiratory disease (with dyspnoea, cyanosis, weight loss, and x-ray changes which may take a year to clear). A few patients have died of pulmonary oedema. In the subacute form there are fine, nodular shadows in the lung fields on radiography, with some disability.

Chronic beryllium poisoning, sometimes called delayed pneumonitis, may occur as a result of remarkably slight exposures to beryllium. Symptoms sometimes occur immediately afterwards, but usually are delayed from weeks to several years. New cases are still occurring, and the maximum time lag is not yet known. Often there is a precipitating event such as a pregnancy or infection. Weight loss is the rule, and it may be very severe; there are also asthenia, dyspnoea, cough, gastrointestinal disorder, and sometimes hyperpyrexia. There is generalized granulomatous involvement of the lungs and liver, and beryllium can be found in these tissues. In some cases there is hypercalcaemia and formation of renal calculi. The prognosis is poor, with remissions and exacerbations: the mortality is 20%, and in those who survive disability is serious. A small minority are asymptomatic. Sometimes chronic disease follows on one or more attacks of acute disease. There is often impairment of liver function, and the serum protein level and calcium-phosphorus metabolism may be abnormal. Diagnosis depends on the demonstration of exposure to beryllium, and is assisted by spectrographic analysis of body fluids or tissues. The only effective treatment is conservative, using oxygen; ACTH has been tried.

In most cases beryllium oxide is the aetiologcal agent, and the bizarre incidence of cases may be accounted for by varying physical characteristics of particles. Beryllium poisoning appears to be a systemic disease, with formation of granulomata in various organs and with irreversible fibrosis following later. The element has a direct toxic action on certain enzyme systems. The author suggests that beryllium is stored harmlessly if absorbed slowly, but may be mobilized and become toxic during other disorders. [The pattern of beryllium
poisoning in U.S.A. has not appreciably altered since the same author first described 17 chronic cases in 1946. More than 180 such cases have now occurred.

J. N. Agate.


Sweden's isolation during the war made it necessary to extend the production of shale oil. In this industry there was considerable exposure to hydrogen sulphide owing to the high concentration of sulphur in the shale layers. Estimation of the air at various places in the workings showed that the concentration of hydrogen sulphide was more than 0·060% in 9 places, more than 0·015% in 11 places, more than 0·002% in 24 places, and less than 0·002% in 62 places. This figure of 0·002% is considered to indicate the maximum concentration allowable for prolonged exposure to the gas.

During the period from 1943 to 1946, 59 cases of acute gas poisoning with unconsciousness occurred at the shale-oil plant, but there were no deaths. The symptoms were a sudden feeling of fatigue, especially in the legs, dizziness, and intense anxiety, followed by unconsciousness with or without respiratory failure. After recovering consciousness the patients complained of pronounced pain in the back of the head, dizziness, and sometimes nausea. The only objective symptoms found on examination were nystagmus and Romberg's sign. In 6 cases there were further sequelae, of which damage to the ear affecting equilibrium was the most prominent. There were also changes of temperament and neurasthenic symptoms, recovery from which took about 2 months, and there was considerable sensitivity to the gas afterwards. Subacute poisoning was characterized by keratoconjunctivitis and irritation of other mucous membranes; no permanent damage to the eyes occurred. There is no positive evidence of chronic hydrogen sulphide poisoning, but the frequency of neurasthenic symptoms increased with the degree of hydrogen sulphide exposure and the length of employment.

K. M. A. Perry.


Potassium bromate is used as a neutralizer in home permanent-wave outfits. Although poisoning due to this substance has been recorded only twice, similar cases may be expected in view of the popularity of these permanent-wave outfits. No bromide or bromine is liberated from potassium bromate on incubation with normal gastric juice at 38° C. for 3 days. Previous workers have described among the toxic effects of bromates vomiting, diarrhoea, depression of the nervous system (particularly the respiratory centre), and gross tubular degeneration of the kidneys.

A 3-year-old boy drank a quarter of the clear fluid contained in a milk-bottle, which contained ½ oz. (14.2 g.) of potassium bromate dissolved in 1 pint (570 ml.) of water. One hour later he complained of nausea, vomited several times, passed 2 fluid stools, and had much abdominal discomfort. Retching started later followed by haematemesis estimated at "half a cupful". Six hours after swallowing the fluid he was admitted to hospital unconscious, pale, and flaccid. The pupils reacted to light but the tendon reflexes were absent, the pulse was 100, and the blood pressure 85/45 mm. Hg. Eyeball tension was diminished, and the tongue was dry although the skin was moist. The respirations were 30 per minute, shallow, and the breath smelled of acetone. The axillary temperature was 97° F. (36.1° C.).

Gastric lavage was performed and 30 oz. (850 ml.) of 5% dextrose given by intravenous drip. Two hours later the pulse was 160 and the blood pressure 110/65 mm. Hg (normal pulse and blood pressure at this age are 105 and 80/60 mm. respectively). Consciousness was regained 3 hours after admission. Intermittent vomiting occurred in the next 3 days. The child was irritable, pale, and motionless. Anuria was present for 24 hours, increasing amounts of urine being passed in the next 2 days. Albumin was present in the urine for 7 days—at first 6 g. per litre. No other abnormal constituents were present except acetone on the second day. The child took an active interest in his surroundings on the seventh day, convalescence was uneventful, and review at intervals during the next month revealed no abnormality, though the mother said he was fretful and irritable.

R. Hodgkinson.


Acute cadmium poisoning is usually manifested by symptoms of respiratory irritation which are severe and often fatal. This paper describes the cases of 5 men, all of whom recovered after illnesses which were more or less mild, and indeed might not be recognized as cadmium poisoning. Short clinical histories are given, together with details of all the biochemical and haematological findings.

All the men were exposed to cadmium fumes or dust, two being metal-burners and 3 being engaged in mixing powders. The 2 metal-burners suffered an acute illness following a single instance of exposure to cadmium. The first developed severe headache and later coma, but recovered consciousness in a short time; his other symptoms disappeared in 3 months. The cadmium content of the blood was 0.18 mg. per 100 g. initially, and this fell to 0.12 mg. per 100 g. after 3 months, but rose again to 0.14 mg. per 100 g. when the patient had a respiratory infection a year later. When this infection subsided, cadmium disappeared from the blood. The second metal-burner developed headache, dizziness, weakness, and pain in the legs after encountering some plated metal in his work. His blood cadmium was 0.12 mg. per 100 g., but after 5 months only a trace was found, and by this time his symptoms had subsided. The third case was that of a man who had worked with coloured powders for 3 years, and had felt tired for some time. Both lead and cadmium were found in the blood and urine, but 6 months after he was removed from exposure he felt well and neither metal was detected biochemically. The fourth victim had been powdering cadmium sulphide for a year without wearing a mask, and developed cough, dyspnoea.
and jaundice. The chest signs cleared up after 3 days, and the jaundice disappeared in a week. The blood cadmium value was 0·38 mg. per 100 g., but this dropped to nil in 3 months. [The patient is said to have been exposed to lead, but no evidence of this is presented.]

The fifth patient developed nausea, abdominal pain, and lassitude after handling powdered cadmium compounds for a year. His liver was “felt well below the costal margin”.

From the laboratory findings it was concluded that in all the cases there was evidence of liver damage and anaemia, while in the third, fourth, and fifth cases there was renal injury in addition. These abnormalities all returned to normal in a few months.

[The evidence of liver damage is highly equivocal and the figures in the original paper should be consulted.]

W. K. S. Moore.


In cyanide poisoning many sulphur-containing substances have a remedial effect, and it is believed that cyanides are eliminated by the body in the form of thiosulphates. Among the substances whose detoxicating effect has been investigated are colloidal sulphur, cystine, and cysteine, reduced glutathione, and sodium hyposulphite. The authors consider that materials with an oxidized component are more effective than those containing reduced sulphur. With these considerations in mind they directed special attention to sodium tetrathionate. All experiments were made with adult rats, and the minimum lethal dose (MLD) was determined; this was found to be 15 mg. per kg. of body weight and caused death in from 10 to 45 minutes.

In assaying the antidote, varying amounts of cyanide were given subcutaneously and the tetrathionate was always injected intraperitoneally at the moment when the animal lay on its side and made no further movement; this preceded the stage of convulsions. In from 1 to 5 minutes after administration the animals got up and in a few moments behaved normally. This happened when 1 or 2 MLD had been given, was less dramatic after 3, and failed entirely after 4 MLD when, even if twice the amount of antidote was given, two-thirds of the rats died. The antitoxic action of the tetrathionate is not strictly proportional to the amount given, and this seems to invalidate the theory of a direct action on the cyanide in vivo.

Experiments showed that hyposulphite was no more effective in cyanide poisoning, weight for weight, than the tetrathionate. In fact, when four times the MLD was given, the latter remedy was more effective, since one-third of the animals survived, but hyposulphite did not save any. When lesser amounts of cyanide than 4 MLD were used, recovery with tetrathionate was more marked and rapid than when hyposulphite was used.

It occurred to the authors that the action of tetrathionate differed fundamentally from that of hyposulphite and might be exercised through the intermediary of glutathione, which it reduces in vivo. Cyanide also acts on it in vitro, and the higher the amount of oxidized glutathione in the tissues, the better can the animals tolerate cyanide poisoning. But this tolerance to the poison must depend on the amount of glutathione available, and this explains the inability to tolerate more than thrice the fatal dose. Experiments were made to investigate this hypothesis. Tetrathionate was given intraperitoneally before cyanide was injected subcutaneously; the protective value of the former was greatest when from 15 to 20 minutes elapsed between the injections. Most of the animals, including those which recovered, showed no sign of disturbance for the first 5 minutes, but were nevertheless distressed for 10 minutes subsequently.

It was found that the state of oxidation of glutathione varied from time to time, a rise being followed by a fall and then by a further rise. This explains the phenomena described, for the concentration of cyanide also has variations; hence the intervals between the appearance of the various symptoms of poisoning.

Further experiments supported the general thesis that there is a first stage, 5 to 10 minutes after the injection of tetrathionate, in which glutathione is oxidized by the former and acts on the cyanide in the blood. In a second stage these changes take place in the tissues and principal organs, such as the liver, kidneys, and muscles.

G. C. Pether.


Polypolypropylene glycols are used industrially as hydraulic-fluid bases and plasticizers. Chemically they are polymers of propylene oxide, which itself possesses little pharmacological activity. On the other hand, the polypolypropylene glycols possess considerable pharmacological activity, particularly in the lower molecular-weight ranges.

Three polypolypropylene glycol mixtures were investigated with average molecular weights of 425, 1025, and 2025. The acute toxicities (LD50) of these mixtures for rats were determined and were found to be, respectively, 2·91 g., 2·15 g., and 9·76 g. per kg. when given by mouth; 0·46 g., 0·23 g., and 4·47 g. per kg. when injected into the peritoneal cavity; 0·41 g., 0·12 g., and 0·71 g. per kg. when injected intravenously. Thus polypolypropylene glycol 1025 proved to be the most toxic of the three, while additional determinations for dipropylene glycol showed that it was much less toxic than any of the polymeric mixtures.

None of the mixtures showed any deleterious action on the skin or in the eyes of rabbits, and only polypolypropylene glycol 425 was absorbed through the skin in sufficient amount to produce toxic signs; inhalation experiments with rats showed that polypolypropylene glycol 425 was moderately toxic, while the other two mixtures were comparatively innocuous.

The toxic manifestations after oral administration to rats included sluggishness, prostration, tremors, and convulsions. Intraperitoneal injection led to narcosis, frothing at the mouth, and tremors, while audible rales.

**ABSTRACTS**

**INDUSTRIAL LUNG DISEASE**


The authors studied the renal function of 20 patients aged 36 to 59 years who had silicosis. Patients with cardiac disease, hypertension, and other serious disease, or with a history of renal disease, were excluded from the series. Six of the patients included had active pulmonary tuberculosis with positive sputum. Albuminuria was found in 4 cases, lipoiduria in 20, reduced ability to excrete dilute urine in 10, and a slight rise in blood urea level in 8. The authors discuss 3 possible mechanisms to account for the changes in renal function: the co-existence with silicosis of cardiac insufficiency, the elimination of silica through the kidneys, and the damaging effect of free silica on the mesenchymal tissues. They quote histological studies said to demonstrate fibrotic changes in the spleen, liver, and kidneys in patients dying from silicosis, and conclude that it is these effects which are responsible for the changes in renal function.


Pulmonary and skin granulomata occur in men exposed to certain beryllium compounds. An attempt was made to produce such lesions by implanting into skin samples of beryllium metal, two kinds of beryllium oxide calcined under different conditions, and two kinds of fluorescent powder containing beryllium oxide, of identical chemical composition but calcined differently. In rabbits and rats no lesions developed. The skin of pigs more nearly resembles that of man: the powder was therefore implanted into pigs’ skin, together with various control implants, and biopsies were taken at intervals from 2 days to 6 months. The initial wounds healed spontaneously. Tissue reactions occurred in the subcutaneous fat immediately below the dermis. Beryllium metal and the two oxide samples produced foreign body reactions of non-specific granulomatos type. The two fluorescent powders produced the typical whorled, collaginous granulomata seen in human berylliosis. The powder calcined for a shorter time at lower temperature gave the more extensive and prolonged reaction. This may have been due to increased solubility of beryllium oxide and to the higher surface : weight ratio of its particles.

Physiological and Clinical Observations at High Altitudes.

Tests were carried out on 8 subjects in the course of a Himalaya expedition in 1950. Observations were made between 2,500 and 5,900 metres, and further observations were later made on the same subjects in Paris, concerning the cardiovascular system, respiratory system, and metabolism, while a few observations were made on the central nervous system and blood (haemoglobin). Investigations were of necessity confined to simple clinical tests and estimations of basal metabolic rate. The results are tabulated.

T. C. D. Whiteside.

The Effect of Oxygen Inhalation at High Altitudes.

In continuation of the above report, the action of oxygen on resting pulse, blood pressure, and respiration, and the effects of oxygen given during exertion, are examined. The author discusses the relative merits, on a high altitude mountain climb, of giving oxygen either at rest, so as to aid recovery, or during exertion.

T. C. D. Whiteside.


The authors sought a method of producing gas bubbles in the periarticular tissues of dogs exposed to simulated high altitude, with a view to clarifying the problem whether the periarticular bubbles demonstrable radiographically in man are intra- or extra-vascular, and, secondly, to test the validity of the concept that the relative resistance of small animals to the effects of decompression is dependent on circulatory factors.

The dogs were taken to altitudes of 40,000 to 50,000 feet (12,190 to 12,540 metres) and were given oxygen at the ambient pressure: radiographs of the thighs and legs were taken at altitude, and a dissection of the tissues was made forthwith. It was found that gas in the veins and arteries, periarticularly, and in the intermuscular fascial planes can be recognized radiographically if the amount is sufficient. In anaesthetized dogs which died after reaching 48,000 feet (14,630 metres), the presence of gas in the veins, in the fascial planes of the thigh, and around the knee-joint was established by x-ray examination and dissection. In anaesthetized dogs resting at altitudes of 40,000 to 48,000 feet (12,190 to 12,760 metres) bubbles were not detected by either technique. Exercise of one limb against a tension spring in 67 anaesthetized dogs at 40,000 to 45,000 feet (12,190 to 13,150 metres) produced gas emphysema or gas embolism in 7 (11%), 3 of which had subcutaneous emphysema. Under the same conditions lowering of the blood pressure by intravenous injection of peptone or sorbital mono-laurate was followed by the uniform collection of gas in the popliteal space, intermuscular fascia, and veins of the lower thigh and legs.

D. H. Sproull.


The critical altitude above which the arterial oxygen saturation of man breathing oxygen at ambient pressure begins to fall is 40,000 feet (12,180 metres). To ensure survival above 45,000 feet (13,715 metres) it is necessary to increase the pressure of the gas around the man (as by a pressure suit), or of that in his lungs (by pressure breathing). The course of events in man breathing against a pressure 60 mm Hg above ambient is described: they culminate in syncope, the result of blood pooling in the systemic veins. Not more than 25% of the total blood volume can be spared in this manner. It was found that syncope occurred earlier the higher the ambient temperature: plethysmographic studies showed that the rate of increase in leg volume during pressure breathing is correspondingly dependent on the ambient temperature. Even if the subject can compensate for the rapid pooling of blood in the limbs, syncope will eventually occur: this is attributed to the haemococoncentration which follows the abnormal distribution of the blood, and is due to loss of plasma water to the extracellular fluid in the area of the pooling. The haemoconcentration is greater at higher ambient temperatures. Over 30-minute periods of pressure breathing at room temperature an approximately linear relationship was found between the percentage decrease in plasma volume (calculated from the packed cell volumes) and the breathing pressure. The loss of effective circulating blood volume, due to the rapid pooling of blood in the systemic veins and the more insidious haemoconcentration, is considered to be the cause of the eventual collapse.

It is concluded that for very high altitude flying some form of emergency pressure suit is a necessity.

D. H. Sproull.