REVIEW ARTICLE

INDUSTRIAL TOXICOLOGY

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MANY chemical substances newly introduced into industry and agriculture are dangerous under certain conditions; how dangerous has, on several occasions, not been realised until a fatal accident has occurred. This review concerns the toxicity of a group of metals (beryllium, cadmium, osmium and vanadium), and of certain highly dangerous substances now widely used as agricultural sprays (dinitro-*o*-cresol and the organic phosphorus insecticides).

BERYLLIUM

Beryllium is a very light metal, having about the same density as magnesium. It is hard and shiny and resembles steel in appearance and lustre. It occurs in nature as beryllium aluminium silicate, or beryl ($3BeO.Al_2O_3.6SiO_2$). Its alloys are important. Beryllium-copper is hard, resistant to corrosion, non-rusting, non-sparking and non-magnetic. It has a tensile strength as great as that of mild steel and 6 times that of copper. Metallic beryllium is employed as a deoxidiser in steel-making. In the atomic energy industry, pure beryllium rods are essential to the efficient working of the graphite pile. Industrial radiography has created a demand for pure beryllium foil for the windows of x-ray tubes; the metal allows the passage of long wavelength radiation. Occupations involving exposure to beryllium compounds include the extraction of the metal from the ore, the preparation of beryllium steel, the manufacture and cutting of beryllium-copper alloys, and the making of beryllium-containing crystals for wireless telephony apparatus. In addition, there may be exposure to beryllium oxide used as a refractory for making crucibles, and to beryl in the manufacture of electrical porcelain. A considerable hazard exists in preparing and mixing the powders used as phosphors for coating the tubes of fluorescent strip lamps and certain tubes used for electric signs. In this industry the compounds used are zinc beryllium manganese silicate, zinc beryllium silicate and beryllium oxide. The tubing is coated on the inside by pumping into it a liquid suspension of the phosphor, excess of which is then drained away. Dry mixing of the powder, spillage of the liquid suspension and the brushing clean of the ends of the tubes may produce considerable amounts of dust.

Symptoms attributable to exposure to beryllium compounds include (i) conjunctivitis, (ii) irritation of the upper respiratory tract, (iii) dermatitis, (iv) subcutaneous granuloma, and (v) acute and (vi) chronic forms of lung disease.

(i). *Conjunctivitis* is frequently associated with dermatitis of the face. It follows exposure to soluble salts of beryllium in industrial plants

where the ore is processed, or where the halides and acid salts are handled. On removal from contact the lesions readily heal.

(ii). *Upper-respiratory disorders.* Exposure to the soluble salts may also cause irritation of the nose and throat, with epistaxis, and swelling and redness of the mucous membranes. Tracheitis and bronchitis may develop, together with anorexia and dyspnœa, and there may be loss of weight. The symptoms and signs clear up completely within 2 or 3 weeks after exposure ceases, and no special treatment is required.

(iii). *Dermatitis* may be severe and may lead to sensitisation. The lesion is usually an œdematous papulo-vesicular eruption, appearing mainly on the exposed surfaces. Healing occurs promptly on removal from contact and is hastened by local treatment of the lesion.

(iv). *Subcutaneous granulomas* occur when beryllium compounds are introduced beneath the skin (Grier, Nash and Frieman[1]). Such lesions may occur in persons who have cut themselves on broken fluorescent lamps. The granuloma may measure as much as 2·5 by 2·0 cm. in diameter. It is necessary to excise the granulomatous mass and to remove completely all beryllium from the lesions; otherwise healing may be delayed.

(v). *Acute pulmonary disease.* The pulmonary lesions are much more serious. The first cases of the acute disease were reported from the United States of America in 1943 by Van Ordstrand, Hughes and Carmody.[2] In 1949 Aub and Grier[3] reported on 7 cases of acute pneumonitis in metallurgical workers exposed to the dust and fume of pure beryllium metal and beryllium oxide. The occurrence of such cases supports the view that the beryllium ion is toxic in its own right, and that the poisonous effects of soluble beryllium salts are not to be attributed to the acid radicals. In 1949 Machle, Beyer and Tebrock[4] reported on more than 400 cases of lung disease which had occurred in beryllium workers in the United States of America. The symptoms of the acute disease are those of a chemical pneumonitis. They occur during employment. In the early stages, cough with blood-stained sputum is accompanied by retrosternal pain, dyspnœa, cyanosis and loss of weight. Non-productive cough may be present for several days before dyspnœa on exertion occurs; later, dyspnœa at rest appears. Rapid respiration, anorexia and marked prostration follow. Usually there is no fever, but cyanosis and tachycardia are present and râles are heard over both lungs. Death may occur within 2 weeks. The morbid anatomy of the lungs is similar to that of acute chemical pneumonitis from other causes, except that there is less evidence of necrosis. The alveoli are filled with exudate composed of œdematous fluid and fibrin containing macrophages. Collections of lymphocytes and plasma cells occur in the septa. In cases in which death has occurred after several weeks there are large areas of fibroblastic proliferation, such as are seen in organising pneumonia. More commonly, resolution begins in the third week of the illness and is complete in from 5 weeks to 5 months. Serious sequelæ are unusual, but attacks of the acute illness have been followed by the onset of chronic berylliosis after 2 years (Machle, Beyer

and Tebrock[4]). Symptoms and signs precede radiological changes in the lungs by several weeks. On the x-ray plate, linear markings and a granular ground-glass appearance, suggesting pulmonary congestion, appear first. The shadows are diffuse, but they may be less marked at the apices and bases owing to compensatory emphysema. Consolidation may follow. As the clinical signs disappear the lung lesion becomes granular and nodular with conglomerate masses. In from 1 to 4 months these masses disappear, leaving residual fibrosis in some cases.

(vi). *Chronic pulmonary disease.* In 1946, Hardy and Tabershaw[5] described cases of a chronic lung disease occurring among employees of a firm manufacturing fluorescent lamps in Salem (Massachusetts). It was the resemblance between these chronic cases and sarcoidosis which led to the designation, Salem sarcoid. This chronic lung disease may be serious and disabling. It is sometimes referred to as "pulmonary granulomatosis of beryllium workers." The first symptoms are variable and may not appear for as long as 6 years after the last exposure to beryllium compounds. The majority of cases have occurred in employees in the fluorescent lamp industry, but 2 laboratory workers and at least 10 people living in the neighbourhood of factories using beryllium compounds have been affected. Less than 5 per cent. of the persons exposed have developed the disease. This suggests that some people are unduly susceptible to the effects of absorption of small amounts of beryllium. Vague ill-health, slight but persistent loss of weight, weakness and lack of energy, or an unusually persistent infection of the upper respiratory tract may herald the onset of the disease. It may be weeks or months before abnormal signs appear in the lungs. Weakness, anorexia and progressive loss of weight, which may be as much as 20 to 30 pounds (9·0 to 13·6 kg.) in a month, become prominent symptoms and persist throughout the illness. Cough with little sputum, worse in the mornings or on exertion, is constantly present; it bears no relationship to the severity of the disease or to the radiographic signs. Dyspnoea is extreme and may be the presenting symptom. Tachycardia, particularly when there is cyanosis, is associated with a normal or low blood pressure. Clubbing of the fingers develops in the later stages. Cardiac failure occurs, increasing the dyspnœa and later causing orthopnœa and œdema of the extremities. Approximately 33 per cent. of the patients die, and 33 per cent. are permanently disabled and remain in great pulmonary distress. The rest lose their symptoms, the lung changes resolving to some extent.

The earliest change in the radiograph is a diffuse finely granular appearance, homogeneously distributed throughout both lungs. The apices and bases are involved. Paratracheal masses and enlarged hilar shadows are seen in many cases. As the disease progresses, fine nodulation appears on a granular background. Confluence of nodules may occur, but it is much less evident than in silicosis. Later there is lobular emphysema, particularly at the apices and bases. Signs of cor pulmonale may develop, and spontaneous pneumothorax, without pleural effusion, has occurred in a few cases. The x-ray appearances alone are not diagnostic.

The pathological findings in chronic berylliosis somewhat resemble those found in sarcoidosis. The lungs are emphysematous, with scattered fine nodules and diffuse interstitial fibrosis. Granulomas are formed within the alveolar spaces by organisation of exudate. They have a fibrinoid centre with peripheral fibrosis and varying degrees of mononuclear infiltration, together with numerous giant cells of the Langhans type. Similar lesions have been found in the skin and subcutaneous tissue, in hilar and axillary lymph-nodes, and in the liver. Mid-zone necrosis is also found in the liver.

Diagnosis depends upon an occupational history of significant exposure to beryllium compounds, a characteristic onset and course of the disease, the x-ray findings, and the presence of beryllium in the urine and tissues. Differentiation from sarcoidosis, chronic miliary tuberculosis, fungous infections, primary pulmonary fibrosis, diffuse nodular silicosis, miliary carcinomatosis, mitral stenosis and siderosis may be difficult. A diagnosis of chronic berylliosis can only be made by considering the whole picture, together with evidence of significant exposure to beryllium compounds.

Treatment is symptomatic. In patients severely affected, oxygen relieves the dyspnœa. Penicillin-streptomycin ærosol therapy has decreased secondary bacterial infection, but has no other beneficial effect. Attempts to increase the rate of elimination of beryllium by means of injections of 2:3-dimercaptopropanol (dimercaprol; B.A.L.) have not been successful, nor has any other therapeutic measure influenced the course of the disease.

In Great Britain in 1949 poisoning by beryllium and its compounds was added to the list of diseases prescribed under the National Insurance (Industrial Injuries) Act, 1946. In the manufacture of fluorescent lamps, halophosphates (which contain no beryllium) must be used in place of the poisonous phosphors formerly used. Preventive measures must be enforced in all industries where beryllium and its compounds are handled. Every effort must be made by engineering methods to keep the atmospheric concentration at the lowest possible level. Protective clothing and adequate laundry services should be provided. Since subcutaneous granulomas have developed in persons who have cut themselves on broken lamps, caution must be exercised in the disposal and salvage of burnt-out fluorescent lamp tubes. Workers at risk should be seen at regular intervals by a doctor and questioned about suggestive symptoms. They should be weighed at monthly intervals, and have their chests radiographed at least once a year. Repeated medical and x-ray examinations must be made of all workers who have unexplained symptoms, particularly when these suggest disease of the respiratory system.

CADMIUM

The natural sources of cadmium (Cd) are the rare mineral greenockite (CdS) and the zinc ores, which contain up to 3 per cent. of cadmium. It is therefore an important by-product of zinc smelting. Cadmium is resistant to corrosion and withstands wear. Because of these qualities the metal and its alloys are used in many manufacturing processes with

the corresponding risk of poisoning. It is a volatile metal and the brown fume of the oxide is produced readily by heat. The principal industrial hazards arise in the smelting of ores, the welding of alloys and the firing and welding of cadmium-plated metal.

In acute poisoning the symptoms include irritation of the eyes, headache, vertigo, nausea, dryness of the throat, cough with constriction and pain in the chest and weakness of the legs (Ross[6]). Delayed effects may follow after an interval of a few hours, and include shivering, sweating, nausea, epigastric pain and severe dyspnœa, which may be aggravated by the development of confluent bronchopneumonia. These severe symptoms are often accompanied by almost complete absence of physical signs in the lungs. A chronic disease may occur in men exposed to small quantities of cadmium in the working atmosphere for long periods. The striking feature of this disease is pulmonary emphysema giving rise to severe dyspnœa on exertion. Chronic rhinitis with complete anosmia is frequently found. Proteinuria, detected by testing the urine with 25 per cent. nitric or trichloracetic acid, occurs in a high proportion of cases. This protein is distinct from both albumen and Bence-Jones protein and has a molecular weight of 20,000 to 30,000 (Friberg[7]). A golden yellow ring develops on the teeth of workers after two or more years exposure and is an index of absorption but not of poisoning by cadmium (Barthelemy and Moline[8]).

In acute cadmium poisoning necropsy has shown hyperæmia of the bronchi, gastro-intestinal tract and kidneys, and in severe cases confluent bronchopneumonia. Necropsy on a case of chronic cadmium poisoning (Baader[9]) showed vesicular emphysema and pulmonary fibrosis, toxic nephrosis and fatty degeneration of the liver. Cadmium was present in all the tissues despite the fact that the patient had not been in contact with cadmium or its salts for four years before death.

When cadmium is heated dangerous quantities of cadmium oxide are formed and volatilised. Therefore in the smelting of cadmium ores, the welding of alloys and the firing of cadmium-plated metal precautions should be taken to remove all fume by means of adequate exhaust ventilation. It has been suggested that cadmium-coated metal should be labelled. While this measure is effective for large pieces it is somewhat difficult to ensure that small objects so coated are labelled. Treatment of cases is symptomatic and directed specifically against pneumonia when it occurs.

Osmium

Osmium (Os) occurs in the platinum group of metals as the alloy osmiridium which is exceptionally hard and is therefore used for the tips of gold nibs of fountain pens. It is also used for electrical contacts, as a catalyst in the preparation of synthetic ammonia and for measuring the rapidity of explosion of gun cotton. Osmium itself is innocuous but the volatile osmium tetroxide, commonly called osmic acid, is slowly formed on exposure of the spongy metal to air. Osmium tetroxide resembles bromine in its very irritating odour, and attacks the nose and

eyes. The vapour has a sudden vigorous irritant effect on the mucosa of the nose, pharynx and bronchi. If high concentrations are inhaled there is a sense of momentary constriction of the chest and inability to breathe; the aftermath may persist for 12 hours (McLaughlin *et al.*[10]).

In severe cases capillary bronchitis and, later, bronchopneumonia may follow inhalation of the vapour (Raymond[11]). Lachrymation may be profuse and the patient may see haloes around bright lights; ulceration of the cornea may occur. In experimental animals extensive bronchopneumonia has occurred and pannus has followed damage to the eye.

Histologists using osmic acid as a stain for myelin and fat are familiar with the headache occurring if the bottle is left unstoppered on the bench. Because of the blackening of osmium tetroxide in contact with oil and fat, an aqueous solution of osmic acid was at one time used for taking finger-prints. The method was abandoned since dermatitis followed its use. Preventive treatment of osmic acid poisoning consists in the proper ventilation of reaction vessels and other apparatus giving off osmium tetroxide. It is clear that the vapour of this substance must not be allowed to enter the atmosphere of the workroom.

Vanadium

The ores of vanadium (V) are patronite, vanadium sulphide, carnotite, potassium uranyl vanadate, and vanadinite, a lead vanadium oxide. In countries where the ores are not found, petroleum residues form the main source of supply. More than 20 tons of vanadium pentoxide are recovered annually from soot which collects in the boilers and smoke-stacks of ships burning Venezuelan and Mexican fuel oil. About 95 per cent. of the world's supply of vanadium is consumed in the manufacture of hard alloy steels. Vanadium pentoxide is used as an oxidising catalyst in the conversion of naphthalene to phthalic anhydride and is replacing platinised asbestos in the contact process for the manufacture of sulphuric acid (Symanski,[12] Sjoberg[13]).

Vanadium poisoning gives rise to conjunctivitis, pharyngitis, bronchitis and even bronchopneumonia. The conjunctivitis may proceed to suppuration. Nasal catarrh is sometimes followed either by atrophic or by hyperplastic changes in the mucous membrane. An allergic dermatitis may be seen. Chronic pharyngitis is responsible for a dry irritating cough but the larynx is rarely inflamed. The worker complains of giddiness, fatigue, and a feeling of constriction in the chest, which is followed by profuse expectoration, and rarely by hæmoptysis. Palpitation occurs on exertion. Examination shows a greenish black discoloration of the tongue, tremor of the upper limbs, and rhonchi throughout the lungs. The pulse may be irregular from extrasystoles. Bronchopneumonia is a frequent complication and may be fatal. Reticulation of the lung fields has been described in x-rays, but there have been no histological reports of pulmonary fibrosis. The sedimentation rate is slightly increased in the uncomplicated case. (Wyers,[14] Sjoberg[13]).

In order to prevent industrial poisoning by vanadium compounds, mechanisation and enclosure of all dusty processes must be strictly enforced.

DINITRO-*o*-CRESOL

This compound is called 3:5-dinitro-*o*-cresol by the Chemical Society of London. It is referred to also as 2:4- or 4:6-dinitro-*o*-cresol. The confusion arises from alternative methods of numbering. It is a yellow crystalline solid manufactured on a large scale as a weed-killer, insecticide, ovicide and fungicide. It was introduced in 1892 as the active constituent of a preparation *antinonnin* used against the nun moth. The work which led to its commercial development was done in 1925 by Tattersfield, Gimingham and Morris.[15] It is applied in agriculture as an aqueous solution of the sodium salt, while for locust control it is used as a dust or as a solution in oil. In 1933 Dodds and Pope[16] recommended it for the treatment of obesity as being more effective and less toxic than dinitrophenol, but in 1937 the dangers from its ingestion were widely recognised and it passed into disrepute.

The actions of dinitro-*o*-cresol and dinitrophenol are qualitatively similar in all respects. The acute lethal effect of each substance is due to excessive stimulation of the general metabolism. Dinitro-*o*-cresol may be considered about twice as active pharmacologically and about twice as toxic as dinitrophenol. A papular dermatitis is common in workers handling dinitro-*o*-cresol and burns of the skin of the hands have been reported (Gate and Chanial[17]). Nasal irritation was noted by an entomologist applying dinitro-*o*-cresol treatment in locust control experiments (Gahan[18]) and both cough and dyspnœa have been complained of by industrial workers after inhaling dinitro-*o*-cresol dust. Although some of the cases reported as jaundice following exposure have been merely the yellow dyeing of the skin due to the compound itself, there seems no doubt that severe liver damage can occur. Neither polyneuritis nor agranulocytosis seem to have been reported as effects of poisoning. The fact that cataract has been recorded only once may be merely a reflection of the less extensive or more cautious use for slimming as compared with dinitrophenol (Horner[19]).

When an animal is given a moderate dose of dinitro-*o*-cresol, say 1 mg./kg. of body weight, the basal rate of metabolism is raised by about 40 per cent. The only abnormalities observed are moderate flushing of the skin and increased pulmonary ventilation. The effect comes on within a few minutes of injection or within 15 minutes when the drug is ingested, and reaches its peak within 1 hour; its duration appears to vary with the size of the animal, being about 2 hours in the rat and from 1 to 4 days in man. With larger doses all the mechanisms of the body which control heat loss are brought into action. If these are inadequate, the temperature rises and remains high until the metabolic rate begins to decline. The increase in metabolism is always much greater than can be ascribed to the fever itself. There is usually hyperglycæmia associated with a fall in liver and muscle glycogen.

When a lethal dose is given the metabolism and the respiratory minute volume may increase to 10 or more times the normal, and the temperature may rise to 105° F. or more. The increase in breathing and in cardiac

output become inadequate to supply the needs of the tissues for oxygen and to carry off the excess of heat and metabolites. Finally death occurs from heat stroke or cerebral œdema, respiration and the heart failing almost simultaneously. Rigor mortis sets in at once. At the moment of death the temperature may exceed 110° F.

Overdosage of dinitro-*o*-cresol, taken for obesity, has caused at least 3 deaths in Great Britain and its industrial and agricultural use at least 9 more. Deaths and cases of severe intoxication in industrial and agricultural workers have been reported from Germany, Hungary, France, the United States of America, India and Africa. The symptoms and necropsy findings in all cases were similar (Bidstrup and Payne[20]). Typically the worker felt ill late in the day, began to sweat profusely and to be very thirsty, went home and lay down but grew rapidly worse with high fever, weakness, anxiety and great hyperpnœa. From 2 to 8 hours after stopping work the fatal heat stroke observed in animals came on, death being preceded by a brief period of coma. Rigor mortis set in immediately. At necropsy the changes noted were yellow pigmentation of all the tissues, dehydration, petechial hæmorrhages of brain and lungs, and parenchymatous degeneration of liver and kidneys. Non-fatal cases of poisoning with dinitro-*o*-cresol have occurred both through medicinal and industrial exposure.

Merewether[21] recorded 14 cases of poisoning which occurred in a factory in Great Britain in 1943 during the height of the summer. For 2 years it had been manufactured in paste form with no harmful effects to the worker, but on this occasion a dust was being prepared for use against locusts. Parsons[22] saw 3 cases of severe intoxication from this group. One was a man aged 37 who had been employed for 17 days pouring the powder from kegs into a grinding mill. He wore a mask but stated that it did not fit well so that he inhaled dust which arose from the mill. In 1 day his hands were stained yellow and in 3 days his feet, ankles and knees were yellow too. He was well until 2 days before admission to hospital. His first symptom was sweating at night. Next day he felt suffocated, became dyspnœic and weak, and believed that his mouth was full of dust. The most striking feature was the profuse sweating. On examination the temperature was 100° F., the pulse rate 130, and the respiratory rate 38 per minute, but no other abnormal physical signs were discovered. There was no tremor nor exophthalmos. The basal metabolic rate, determined 24 hours later, was 180 per cent. He recovered completely within 48 hours. After the introduction of locally applied exhaust ventilation and periodic medical examination of workers in the factory concerned, only one further case of mild severity was reported (Merewether[21]).

McDonald[23] reported the case of a negro factory worker whose palms and soles were yellow and who recently had lost 20 lbs. weight. He had a temperature of 102° F., a phenomenal basal rate of metabolism of 400 per cent., rapid pulse, rapid respiration, profuse sweating, shortness of breath and cough. An examination of his place of work showed that he had been exposed to 4·7 mg. of dinitro-*o*-cresol dust per cubic metre

of workroom air per day. The man recovered. Pollard and Filbee[24] recorded a case of acute poisoning with recovery in a spray operator who had been applying dinitro-*o*-cresol to cereal crops. On the twelfth day after the patient had been admitted to hospital, and 7 days after he was free from symptoms the basal metabolic rate was still 180 per cent.

Dinitro-*o*-cresol is a cumulative poison in man and is eliminated slowly. It is possible to correlate physiological effects with the concentration of dinitro-*o*-cresol in the blood (Harvey, Bidstrup and Bonnell[24]) and routine estimation of the blood level in persons at risk should be included among the measures adopted for the prevention of poisoning. Dinitro-*o*-cresol can be estimated accurately in 0·1 ml. of blood obtained by finger-tip or ear-lobe puncture using the method described by Parker[25] adapted by Harvey.[26]

The earliest symptom of dinitro-*o*-cresol poisoning is an exaggerated feeling of well-being, but this is difficult to assess. It is likely to be present when the concentration in the blood is of the order of 20 μg./g. of blood. Unusual thirst, excessive sweating and fatigue are late manifestations of poisoning. They are frequently attributed to other causes such as hot weather and long hours of work. Since most spray operators lose weight during the cereal crop spraying season, loss of weight is also unreliable as a warning sign of poisoning.

Measures adopted to reduce the incidence of poisoning include periodic medical examination of workers, the introduction of locally applied exhaust ventilation in factories, and the use of protective clothing and enclosed tractor cabins by spray operators. The ideal tractor cabin is gas-proof, air conditioned, and water cooled and is designed in such a way that it will not operate with the door open. Although dinitro-*o*-cresol is absorbed through the skin, relatively small amounts gain entrance to the body by this route, and in the cases of poisoning recorded, inhalation of spray mist or dust has been the most likely method of absorption. Some form of respirator should therefore be worn by all persons at risk of absorbing dinitro-*o*-cresol through the respiratory tract, and is an essential part of protective equipment for men spraying cereal crops and for supervisors and all other persons who come into the vicinity of spraying operations.

Individual workers have different methods of handling dinitro-*o*-cresol both in mixing the spray and in correcting faults such as blockage of the nozzles on the spray boom. Mixing and spraying should be done across wind so that spray and dust are carried away from the operator. Modifications of standard spraying equipment result in different degrees of risk. Spraying machines working on an atomiser principle seem to be particularly dangerous since they produce a fine spray which drifts easily and settles as a dust which flies readily. Often there is no agitator in the spray tank to keep the dinitro-*o*-cresol in suspension, and the nozzles of the spray boom frequently become clogged. A spray operator on such a machine was observed during most of one day to correct this fault by jumping from the moving machine, running into the spray, and hitting blocked nozzles with a spanner while the machine and spraying continued.

This is specifically forbidden by his employers but adequate supervision of individual workmen in this type of work is difficult to arrange. In one fatal case it was discovered that the man had quenched his thirst with water contaminated with dinitro-*o*-cresol.

The workmen are warned that they are handling a dangerous substance, and spray crews are instructed in spraying methods and in the early symptoms and signs of poisoning. In spite of these precautions poisoning still occurs and may prove fatal within a few hours of the onset of symptoms (Steer[27]). The Agricultural (Poisonous Substances) Act, 1952, places upon the employer responsibility for providing adequate means of protection from absorption of dangerous amounts of dinitro-*o*-cresol and other toxic chemical substances used in agriculture, and for ensuring that these precautions are carried out by all members of spraying teams.

As a result of experimental work on volunteers (Harvey, Bidstrup and Bonnell[24]) and the estimation of dinitro-*o*-cresol in single samples of blood collected from men engaged in its manufacture or in its use as a late winter wash on fruit trees or as a selective weed-killer in cereal crops (Bidstrup, Bonnell and Harvey[28]) it is possible to state that when the concentration in the blood is about 20 μg./g. of blood or more, the man should be removed from further contact with dinitro-*o*-cresol for at least 6 weeks. To avoid false high or "peak" values, the blood should be collected not less than 8 hours after the last exposure. Since the workman will have no symptoms he may continue to work provided he does not handle any substance known to be toxic.

When the blood dinitro-*o*-cresol level is between 10 and 20 μg. the man may continue to work, but close supervision is necessary to ensure that he obeys strictly all the precautions recommended for the safe handling of dinitro-*o*-cresol. The blood estimation should be repeated in 48 hours and if there is any increase, the man should be removed from further contact. The exaggerated feeling of well-being is likely to be present when the blood level is above 15 μg. but unless the workman is well-known to the observer, this change is difficult to assess. If the blood concentration is less than 10 μg. the man may continue at work and no extra precautions need be advised.

No antidote to dinitro-*o*-cresol is known. Early diagnosis is essential and treatment on general lines will result in recovery, even in seriously poisoned patients. The patient must be kept cool by tepid sponging; fluids and electrolytes which are lost in the profuse sweating which characterises the illness in its acute stages must be replaced; barbiturates should be administered in doses adequate to allay the anxiety which is also a striking feature of dinitro-*o*-cresol poisoning.

Organic Phosphorus Insecticides

Modern methods for the control of insect pests such as aphis and red spider include the use of insecticides in which the active substances are organic compounds of phosphorus. Preparations in common use contain tetra-ethylpyrophosphate (TEPP), hexa-ethyltetra-phosphate (HETP), diethyl-*p*-nitrophenylthiophosphate (*parathion*, E. 605.f.,

DPTF, or *bladan*) and octamethyl pyrophosphoramide (*Schradan* or OMPA). The first work on these compounds was carried out in Germany in 1939. They are related in chemical structure and physiological action to di-*iso*propyl-fluorophosphate (DFP) which is a powerful cholinesterase inhibitor used in the treatment of myasthenia gravis, paralytic ileus and glaucoma. The insecticidal properties of TEPP, HETP and *parathion* are similar to those of nicotine. The effects of HETP are almost certainly due to contamination by TEPP of the manufactured product. *Schradan* is a systemic insecticide, that is to say it has no direct insecticidal action nor is it an inhibitor of cholinesterase *in vitro*. It is converted in the plant or animal tissues and is effective as an insecticide only against pests which eat the plants. Early in 1945 when there was a world shortage of nicotine a pilot plant for the production of organic phosphorus insecticides was built in Leverkusen. Soon after the end of the Second World War the manufacture of these insecticides was started in the United States of America and in Great Britain. Preparations include liquid sprays, dusts and wettable powders which are diluted before being applied in greenhouses, orchards and fields.

Insecticides containing organic compounds of phosphorus are poisonous to man and animals. In a single dose they are less toxic than nicotine, but the effects of absorbing small amounts of these anticholinesterase substances are prolonged and result in increased susceptibility to absorption of further amounts of any cholinesterase inhibitor. All types of preparation penetrate rapidly through the skin producing only slight irritation at the site of absorption. Exposure to as little as 0·3 g. daily has been estimated as dangerous to man. The lethal dose by mouth for man is approximately 100 mg. of TEPP or *parathion* and symptoms follow the administration of more than 10 mg. (DuBois[29]). Absorption may also occur from inhalation and ingestion. The early symptoms of poisoning are mild and non-specific and may include headache, nausea, anorexia and unusual fatigue. These may be accompanied by pin-point constriction of the pupils. The symptoms are aggravated by smoking or taking food. From 2 to 8 hours later nausea, abdominal cramps, vomiting, diarrhœa, muscular twitching, coma, convulsions and signs of pulmonary œdema may develop. Incontinence of urine and fæces is common. Death may result in as short a time as 1 hour after the onset of symptoms. Atropine is an antidote to the muscarinic and central nervous system effects of this form of poisoning. It should be given in doses of 1 to 2 mg. (1/60 to 1/30 gr.) at hourly intervals until the pupils are dilated. Oxygen, under slight pressure to overcome bronchial spasm, should be administered at the first sign of pulmonary œdema. The fibrillary twitching of muscles appears to affect particularly the diaphragm, and artificial respiration may be necessary. This effect upon striated muscle is due to the nicotine-like action of these compounds. No antidote to this effect is known and death may occur from neuromuscular paralysis even though the muscarine-like effects and the signs of involvement of the central nervous system have been controlled by atropine.

HETP and TEPP hydrolyse rapidly in the presence of water or alkaline solutions. Danger of poisoning from these two substances is most likely to occur when the concentrated materials are handled in manufacture or in mixing with suitable wetting agents. *Parathion* is more stable and 168 cases of poisoning, 7 of them fatal, were reported from the United States of America in 1950. (Committee on Pesticides Report[30]).

Strict precautions are necessary to protect workers engaged in handling these insecticides. Protection is more easily arranged and applied in factories than in field operations. In factories where organic phosphorus insecticides are made, mixed with wetting agents, or incorporated in dusts or wettable powders exhaust ventilation should secure that this substance is absent from the atmosphere. Protective clothing must include overalls, gloves, boots, cap and underwear which are laundered each day, and changed immediately if accidentally splashed. Ordinary clothing must be protected from possible contamination. Respirators should be available in factories for use in emergency; in field operations they must be worn during dusting operations and the diluting of wettable powders. It is necessary that the workers should wash thoroughly before eating or smoking, and a bath should be taken at the end of a day's work. These instructions together with an account of the symptoms of poisoning must appear on the labels of containers. The attention of all workers exposed to risk should be directed repeatedly to the toxic properties of these compounds. The protective measures should be emphasised and enforced.

Absorption of TEPP, *parathion* and *Schradan* results in depression of the cholinesterase action of both red blood cells and serum before symptoms or signs of poisoning occur. People at risk should have the blood cholinesterase activity estimated at frequent intervals. The normal range of cholinesterase activity for the general population has been determined (Callaway, Davies and Rutland[31]) and the finding of a lowered cholinesterase in a workman who has been handling organic phosphorus insecticides in a factory or in the field is an indication for removing him immediately from further exposure. He should not be allowed to return to work with these substances until the cholinesterase activity has been shown to be within normal range.

The statement that there are no sequelæ to poisoning by organic phosphorus compounds used as insecticides has proved to be erroneous. In Great Britain 3 people developed acute poisoning while engaged on a pilot plant in the manufacture of a new substance in this group, bis-mono-*iso*propyl aminoflurophosphine oxide. Recovery from the acute phase of the illness followed the administration of atropine in large doses, but in the third week after the onset of symptoms 2 of the patients developed paralysis of the limbs similar to that which follows poisoning by tri-*o*-cresyl phosphate. Petry[32] has described this type of paralysis following repeated exposure to *parathion* in the fumigation of greenhouses in Germany. People who have had acute poisoning by organic phosphorus compounds should be kept under close observation until the cholinesterase activity of the blood has returned to normal.

REFERENCES

Beryllium.
1. Grier, Nash and Freiman, *J. Industr. Hyg.*, 1948, **30**, 228.
2. Van Ordstrand, Hughes and Carmody, *Cleveland Clin. Quart.*, 1943, **10**, 10.
3. Aub and Grier, *J. Industr. Hyg.*, 1949, **31**, 123.
4. Machle, Beyer and Tebrock (1949). *Proc. Ninth Internat. Congress Industr. Med.*, London, 1948, p. 615. Wright, Bristol.
5. Hardy and Tabershaw, *J. Industr. Hyg.*, 1946, **28**, 197.

Cadmium.
6. Ross, *Brit. med. J.*, 1944, **1**, 252.
7. Friberg, *Acta. med. scand. Supp.*, 1950, 240.
8. Barthelemy and Moline, *Paris méd.*, 1946, **36**, 7.
9. Baader, *Dtsch. med. Wschr.*, 1951, **76**, 14, 484.

Osmium.
10. McLaughlin, Milton and Perry, *Brit. J. industr. Med.*, 1946, **3**, 183.
11. Raymond, *Progr. med., Paris*, 1874, **2**, 373.

Vanadium.
12. Symanski, *Arch. Gewerbepath. Gwerbehyg.*, 1939, **9**, 295.
13. Sjoberg, *Acta med. scand.*, 1950, **138**. Supp. 238.
14. Wyers, *Brit. J. industr. Med.*, 1946, **3**, 177.

Dinitro-o-Cresol.
15. Tattersfield, Gimingham and Morris, *Ann. appl. Biol.*, 1925, **12**, 218.
16. Dodds and Pope, *Lancet*, 1933, **225**, 352.
17. Gate and Chanial, *Bull. soc. franc. Derm. Syph.*, 1936, **43**, 1305.
18. Gahan, *J. Econ. Entom.*, 1942, **55**, 669.
19. Horner, *Tr. Amer. Ophth. Soc.*, 1941, **77**, 405.
20. Bidstrup and Payne, *Brit. med. J.*, 1951, **2**, 16.
21. Merewether, *Annual Report of the Chief Inspector of Factories, London*, 1943, p. 51, Cmd. 6563.
22. Parsons, 1948, *Personal Communication.*
23. McDonald, *Baltimore Health News*, 1943, **20**, 9.
24. Harvey, Bidstrup and Bonnell, *Brit. med. J.*, 1951, **2**, 13.
24. Pollard and Filbee, *Lancet*, 1951, **261**, 618.
25. Parker, *Analyst*, 1949, **74**, 646.
26. Harvey, *Lancet*, 1952, **262**, 796.
27. Steer, *ibid.*, 1951, **260**, 1419.
28. Bidstrup, Bonnell and Harvey, *Lancet*, 1952, **262**, 794.

Organic Phosphorus Insecticides.
29. Dubois, *Proceedings, 9th International Congress of Entomology. Amsterdam*, 1951. (*In the press.*)
30. Committee on Pesticides of the American Medical Association Council on Pharmacy. *J. Amer. med. Ass.*, 1950, **144**, 104.
31. Callaway, Davies and Rutland, *Brit. med. J.*, 1951, **2**, 812.
32. Petry, *Zbl. Arbeitsmed. Arbeitsschutz*, 1951, **1**, 86.