ment of spot area, this being related to the amount of material present (Purdy & Truter, 1962).

Among other devices that have been investigated in this Centre, mention should be made of a machine that uses a flame ionization detector for detection and quantitative determination of t.l.c. spots on quartz rods coated with silica gel (Padley, 1969). Good results were obtained with sample loadings of 1–10 µg,

the main difficulties encountered being concerned with application of the sample without dislodging the coating and retention of developing solvent on the coating after supposed drying.

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PHARMACOLOGICAL BIOCHEMISTRY GROUP COLLOQUIUM ON 'MERCURY INTOXICATION'

Clinical Symptoms of Mercury Poisoning in Man

By P. LESLEY BIDSTRUP (11 *Sloane Terrace Mansions, Sloane Terrace, London SW1X 9DG, U.K.*)

Mercury vapour, inorganic compounds of mercury and organic compounds of the aryl series, such as phenylmercuric acetate, produce symptoms and signs that differ significantly from those caused by absorption of short-chain alkylmercury compounds (ethyl and methyl derivatives).

Mercury and the inorganic compounds. The soluble inorganic mercury compounds, particularly HgCl_2 , are irritating to skin and mucous membranes (Sollman, 1957), and absorption from the skin may be sufficient to cause systemic poisoning. Some people are particularly susceptible, collapse and serious illness resulting from therapeutic doses of Hg_2Cl_2 (calomel) (Martindale, 1958). Slow absorption of insoluble compounds through the skin may occur, and mercury dermatitis in the red areas of tattoo [HgS (cinnabar)] has been reported (Keiller & Warin, 1957).

Since HgCl_2 has become less popular as an agent for homicide or suicide, acute systemic mercury poisoning is seldom seen. Characteristic features were coagulation, irritation and superficial corrosion of tissues at points of contact, rapidly fatal circulatory collapse or delayed death from renal tubular necrosis. Haemorrhages, congestion and ulceration of the large intestine were found also at necropsy. Pink disease (acrodynia) of infants is attributed by some authorities to hypersensitivity to inorganic mercury present as Hg_2Cl_2 in anthelmintics and teething powders (Warkany & Hubbard, 1953). Exposure to high concentrations of mercury vapour results in lung irritation (Matthes *et al.*, 1958).

Metallic mercury and its inorganic compounds are used in many industries. In the early days acute or sub-acute poisoning, characterized by stomatitis, gingivitis, excessive salivation, loss of teeth, gross tremor with ataxia and serious mental disturbance, was not uncommon, for example, among mirror-

makers, mercury miners and others. Today, chronic mercury poisoning is seen among persons employed in a variety of occupations: the manufacture and servicing of scientific equipment, including thermometers, barometers and mercury-arc rectifiers, the cleaning and packing of mercury or mercury compounds and the manufacture of dry-cell batteries are examples. The common symptoms are erethism (manifested by nervousness, irritability, a tendency to blush readily and change of temperament) and tremor. The pathological lesion has not been identified. Absorption is mainly from inhalation of vapour, droplets or dust, but occurs also through the skin. Symptoms subside on removal from exposure; recovery may be hastened by administration of *N*-acetyl-D-penicillamine 250mg four times daily (q.d.s.) by mouth.

Proteinuria may occur, as may the nephrotic syndrome. The latter is relatively rare, considering the numbers of persons at risk of absorption of mercury. The mechanism is not understood; hypersensitivity has been postulated, but it could well be an as yet unidentified abnormal metabolic pathway. Other signs of mercury poisoning are usually absent from those who develop the nephrotic syndrome. The clinical manifestations of inorganic-mercury poisoning are discussed and occupations entailing exposure to mercury described by Bidstrup (1964). Goldwater (1964) reports on studies of the absorption and excretion of mercury in man. The excretion of mercury in the urine collected over 24h is a valid index of absorption, particularly on a group basis, but is not diagnostic of poisoning. 'Normal' output in non-exposed persons is less than 25 µg/l; in those at risk of absorption considerable fluctuation in mercury excretion occurs from day to day.

Organic compounds of mercury. Because the short-chain alkyl compounds of mercury, such as the ethyl and methyl derivatives, have proved to be extremely toxic to man and animals, it has been usual to condemn all organic mercury compounds. In fact, the aryl compounds, such as phenylmercuric acetate, have been used extensively in the past as fungicidal

and bacteriostatic agents for therapeutic purposes, and in industry and agriculture as fungicides in glass-house crops and as slimicides in paper-pulp mills. They, and other organic mercury compounds, may irritate the skin, causing redness, irritation and blistering, but the systemic effects are few and are different from those characteristic of the short-chain alkyl compounds. Distribution in the tissues of experimental animals is similar to that of metallic mercury and the inorganic compounds (see below).

It should not be forgotten, also, that until recent years organic mercury compounds (mainly mercurated allyl derivatives) were used as diuretics. Toxic effects were rare; Leff & Nussbaum (1957) record total doses ranging from 6240 to 78 560 mg in patients who showed no evidence of harmful effects that could be attributed to mercury.

The short-chain alkylmercury compounds, e.g. the ethyl and methyl derivatives, are exceedingly toxic. They are used mainly as seed dressings to control fungus infection, and in bulb or potato-tuber dipping. They act selectively on the central nervous system and on sensory peripheral nerves. The long spinal tracts are affected, as are the granule-cell layer of the neocerebellum and the area striata of the occipital cortex (Hunter *et al.*, 1940). Degeneration in peripheral sensory nerves that ascends rapidly to the dorsal roots has been demonstrated by Cavanagh (1969).

The clinical picture of poisoning by short-chain alkylmercury compounds is one of bizarre neurological disorder; in advanced cases serious or total disability occurs, due to severe generalized ataxia, dysarthria and concentric constriction of the visual fields. The latter is due to a cerebral-cortical lesion, the fundus oculi appearing normal on retinoscopy (Höök *et al.*, 1954). Experiments suggest that chromosome abnormalities may be caused by absorption of alkylmercury compounds; the significance of observed chromosome breakage in persons eating fish contaminated with methylmercury is not known (Skerfving *et al.*, 1970).

Outbreaks of poisoning involving many hundreds of people have been reported after accidental ingestion of food contaminated by alkylmercury compounds. Jalili & Abbasi (1961) reported 600 cases, many fatal, after consumption of home-made bread prepared from flour made with grain that had been treated with an organomercurial fungicide, and a similar episode has been reported recently from

northern Iraq. In Minamata Bay high concentrations of methylmercury in fish caused many cases of poisoning among the inhabitants, cats and waterfowl who ate fish or shellfish caught from the Bay. Effluent from a process for the manufacture of acetaldehyde that used mercury as a catalyst contained trace amounts of methylmercury that were concentrated 100-fold or more in the aquatic flora on which the fish fed (McAlpine & Araki, 1958; Ui, 1966). It is known, now, that certain micro-organisms can convert inorganic mercury into organic forms by methylation (Jensen & Jernelöv, 1969), and it follows that, in areas where mercury accumulates in fish-rearing waters, high concentrations of methylmercury may be found in fish caught from these waters (*Methyl Mercury in Fish*, Report from an Expert Group, 1971).

Distribution. The distribution of inorganic, aryl- and alkyl-mercury compounds in experimental animals has been studied by many investigators using compounds labelled with ^{203}Hg . A detailed review of present knowledge is included in *Methyl Mercury in Fish* (Report from an Expert Group, 1971). In summary, inorganic and phenylmercury compounds are found in kidney > liver > spleen > muscle > blood, disappearing rapidly from all tissues except the kidney. No significant differences in distribution are reported.

Fukuda (1971) found that elemental mercury is retained in the brain in greater concentration than is the case after administration of the Hg^{2+} ion, and observed tremor in rabbits exposed to mercury vapour. Ethyl and methyl compounds accumulate in higher concentrations in all tissues, particularly in the brain, and are excreted much more slowly. The experimental results are supported by the determination of mercury in tissues in fatal cases of mercury poisoning reported by Kurland (1960), who found 5–20 times as much mercury in the brain in cases of alkylmercury poisoning compared with poisoning by HgCl_2 .

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Pathological Effects of Mercury

By W. H. BUTLER (*Toxicology Unit, Medical Research Council Laboratories, Woodmansterne Road, Carshalton, Surrey, U.K.*)

For centuries mercury has been recognized as toxic. The lesions induced are related to the class of mercury compound administered and to a smaller extent to the species. Inorganic mercury (HgCl_2) causes acute damage to the gastrointestinal tract when given by mouth and, if the animal survives, necrosis of the proximal tubule of the kidney. After a single dose the acute renal damage is rapidly repaired, but repeated treatment causes fibrosis of the kidney (Dieckmann & Butler, 1970). In man repeated doses of the mercurial diuretic mersalyl {sodium *o*-[(3-hydroxymercuri-2-methoxypropyl)carbamoyl]-phenoxyacetate} may induce a nephrotic syndrome (Riddle *et al.*, 1958). The effects of methylmercury on the central nervous system have received much attention since the description of Minimata disease (Harada, 1968) and also poisoning from dressed grains (Jalili & Abbasi, 1961). Earlier Hunter & Russell (1954) described cortical and cerebellar necrosis as a result of industrial exposure. In the rat a similar pattern of damage is seen, affecting the cerebellum and sensory pathways, although, however, cortical lesions are not seen. The distribution of lesions differs from that of organophosphorus compounds, in that the entire sensory pathway is involved whereas in poisoning by organophosphorus compounds a dying back of sensory nerves from the periphery is seen.

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The Biological Properties and Distribution of Mercury

By T. W. CLARKSON (*Departments of Radiation Biology and Biophysics and of Pharmacology and Toxicology, The Medical School, University of Rochester, Rochester, N.Y. 14620, U.S.A.*)

The high affinity of mercuric cations for thiol groups imposes a severe logistics problem in considering the biochemical mechanisms of action of mercurial compounds. To quote from a recent review by A. Rothstein (paper presented at the 4th. Rochester Conference on Toxicity at the University of Rochester, Rochester, N.Y., U.S.A., in 1971) 'although the mercurials are highly specific to -SH groups, they are highly unspecific in terms of proteins. Almost all proteins contain -SH groups that are metal reactive. Furthermore, because -SH groups are important to most protein functions, mercurials can disturb almost all functions in which proteins are involved. Thus almost every protein in the body is a potential target'. In other words the mercurials are potent but unspecific enzyme inhibitors. Thus the view has developed that biochemical and cellular injury will be seen wherever mercury accumulates in sufficient concentrations, a view that has influenced much of the experimental work on the toxicology of mercury compounds. Thus considerable emphasis has been placed on studies of the kinetics and mechanism of transport and distribution of mercury. It is of interest to see to what extent this approach has been useful in leading to a better understanding of the toxicology of mercury.

Quantitative description of the processes of absorption, distribution and excretion have been greatly facilitated by the introduction of γ -ray scintillation counting making use of the isotopic tracer ^{203}Hg (Rothstein & Hayes, 1960). Compartmental analysis of the data revealed an important general property applicable to all mercury compounds studied to date, namely that, in experimental animals given repeated single doses of radioactive mercury, each dose behaved independently of the previous dose with respect to its kinetic parameters. This property greatly simplified mathematical treatment of the data. It allowed calculation of the cumulative body burden of mercury during chronic exposure, the determination of biological half-times of mercury and the efficiency of pulmonary and gastrointestinal absorption. Thus Rothstein & Hayes (1964) were able to determine the pulmonary absorption of mercury vapour to be 100%. The gastrointestinal absorption