

[HEALTH HAZARDS IN INDUSTRY AND AGRICULTURE]
by

P.L. BIDSTURP

Doctor of Medicine
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Telephone:
B1Shopsgate 3255



RESEARCH LABORATORIES,
THE LONDON HOSPITAL,
ASHFIELD STREET,
WHITECHAPEL,
LONDON, E.1

26th August, 1957.

The Dean,
The Faculty of Medicine,
University of Adelaide,
North Terrace,
Adelaide,
South Australia.

Dear Sir,

I declare that the published work which I am submitting for consideration for the degree of M.D. (Adelaide) is my own composition.

The papers report original work on the incidence of carcinoma of the lung among workmen employed in the bichromates-producing industry in Great Britain, and on the effects of poisoning by dinitro-ortho-cresol and organic phosphorus compounds. It has been shown that an occupational risk exists for persons employed in the bichromates-producing industry, and for spray operators who use dinitro-compounds or organic phosphorus compounds in agriculture and horticulture. Methods of reducing the risks have been suggested, and in the case of the dinitro- and organic phosphorus compounds, the recommendations made in the published papers submitted form the basis of the regulations under the Agriculture (Poisonous Substances) Act, 1952.

The following summary indicates wherein the investigations reported advance medical knowledge and practice, provides a brief history of the progress of medical knowledge in the subjects of the thesis and indicates the extent to which I am indebted to persons who are joint authors of some of the papers submitted.

1. Carcinoma of the Lung in Workmen in the Bichromates-producing Industry.

Papers 1, and 2 are those reporting the results of an investigation into the incidence of carcinoma of the lung in men employed in the bichromates-producing industry in Great Britain. When the investigation was started in 1948 there was no evidence that carcinoma of the lung was an occupational hazard of the bichromates-producing industry in Great Britain, although studies in Germany and

the United States of America had demonstrated the risk for the industry in those countries. The work reported in my papers demonstrates conclusively that the hazard exists also for the industry in Great Britain. As a result working conditions have been altered in the factories concerned and certain protective measures, including a medical service have been introduced. It is hoped that the measures which have been adopted will result in the future in the incidence of carcinoma of the lung in workers in this industry being no higher than in the general population.

I have planned further investigations which are proceeding under my supervision in an attempt to identify the carcinogen.

I was responsible for planning and carrying out the investigation and am indebted to Dr. R. A. M. Case, joint author of the second paper, only for the statistical analysis of the data obtained during the six-year period of the investigation.

2. Papers on Poisoning by Dinitro-ortho-cresol (4, 5, 6, 7, 11).

Experimental work and experience in the therapeutic use of dinitro-ortho-cresol (DNOC) and the related compound, dinitrophenol for the treatment of obesity between 1933 and 1937 had demonstrated that these compounds caused an increase in the basal metabolic rate which was not due to stimulation of the activity of the thyroid. Later investigations have shown that the acceleration of metabolic processes is due to an effect on intra-cellular metabolism in which the transfer of phosphate is interrupted, making available to the cell respiratory mechanism increased amounts of inorganic phosphate and adenine nucleotide (Judah, reprint no. 11, p. 574.)

Because of fatalities and cases of serious poisoning reported from all countries where DNOC and dinitrophenol had been used in the treatment of obesity, the therapeutic use of these substances was abandoned in 1937. At that time it had not been suggested that repeated small doses of DNOC might have a cumulative effect. My studies of the records of fatal cases of poisoning among men spraying DNOC as a selective weedkiller in cereal crops caused me to put forward this theory. I then planned experiments on human volunteers and collected data relating to the concentration of DNOC in the blood of men engaged in the manufacture and field-use of DNOC.

It was possible to show from these studies that the effects of DNOC absorbed in small amounts over a period of time were cumulative, resulting in the sudden onset of symptoms which progressed rapidly causing death within a few hours, and also that, by estimating the concentration of DNOC in whole blood, men at risk could be removed from further exposure to DNOC before any symptoms developed. It is now common practice to adopt routine estimation of blood DNOC concentration as a measure of the degree of absorption of DNOC in persons working with this material and no deaths nor serious cases of poisoning have occurred in Great Britain since 1951.

I am indebted to Dr. D. G. Harvey for biochemical studies, to Dr. J. A. L. Bonnell for assistance in the clinical examinations, and to Dr. D. J. H. Payne for carrying out the post mortem examinations in cases 7 and 8, reprint no. 5.

3. Poisoning by Organic Phosphorus Compounds (8, 9, 10, 11).

These papers describe the effects of poisoning by organic phosphorus compounds, particularly those used as insecticides (8) and report two cases in which paralysis developed as a sequel to acute poisoning by a new organic phosphorus compound, mipafox (9). That such paralysis might occur following poisoning by these compounds was predicted by Gilman in 1950 (personal communication) because of his experience with compounds of this nature during the 1939-45 War, and his knowledge of the delayed effects following poisoning by tri-ortho-cresyl phosphate (TOCP). Acute poisoning by TOCP is commonly followed by paralysis which may be permanent and in most recorded cases has resulted from the ingestion of food which has become adulterated with TOCP. Poisoning of occupational origin due to TOCP in a patient under my care since 1950 is described (10).

Organic phosphorus compounds inhibit, usually irreversibly, the enzyme cholinesterase and the acute symptoms of poisoning are attributed to this effect. Some of these compounds have been shown to cause demyelination in experimental animals, and the clinical and laboratory evidence in the cases reported support the view that the delayed effects of poisoning both by mipafox and by TOCP are due to a demyelinating process. As a result of the occurrence of paralysis due to mipafox, which was considered after routine toxicity testing to be much less toxic than some organic phosphorus compounds already in use, it is now the custom to test by carefully planned experiments all new compounds of this group to ensure that those capable of causing permanent disability are not brought into use as insecticides. No other cases have been reported in Great Britain or other countries since 1951.

I was responsible for the management and investigation of the patients poisoned by mipafox during the chronic phase of their illness. I am indebted to Dr. J. A. Bonnell for assistance and to Dr. A. G. Beckett, the other joint author, who looked after these patients during the acute phase, and kindly invited me to see them on one occasion during this phase.

With regard to the paper on Anticholinesterases (10) I am indebted to Dr. J. A. Bonnell for helpful criticism during the preparation of the paper which records the delayed effects of poisoning by two cholinesterase inhibitors, mipafox and TOCP, in patients under my care. As I was prevented unexpectedly from attending the Symposium, Dr. Bonnell read the paper for me and took part in the discussions which followed.

The Dean

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26th August, 1957.

The investigation into the effects of dinitro-ortho-cresol and the organic phosphorus compounds used as insecticides, and the precautions which were recommended in the published papers which are submitted, form the basis of the regulations made under the Agriculture (Poisonous Substances) Act, 1952. This is the first Act to be placed on the Statute Book to provide protection for agricultural workers against poisoning resulting from their work, although persons employed in factories have had such protection by means of the provision of the Factories Acts (1937 and 1948) for many years.

4. Papers on Miscellaneous Subjects.

Three publications (12, 13, 14) on miscellaneous subjects in the field of industrial toxicology are also submitted.

Yours faithfully,

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Carcinoma of the Lung in Persons employed in the
Bichromates-producing Industry in Great Britain

- Carcinoma of the Lung in Chromates Workers. Bidstrup,
P.L. (1951) Brit. J. industr. Med. 8, 298. 1
- Carcinoma of the Lung in Workmen in the Bichromates-
producing Industry. Bidstrup, P.L. & Case, R.A.M.
(1956) Brit. J. industr. Med. 13, 260. 2
- Cancer of the Lung in Nickel, Arsenic and Chromate
Workers. Bidstrup, P.L. (1950) Arch. belges. Med.
soc. 500. 3

Poisonous Substances used in Agriculture

- The Health Hazards of Di tro-ortho-cresol. Bidstrup,
P.L. (1949) Proc. 2nd Int. Congr. Crop Protect.
Sections 3 & 4. 4
- Poisoning by Dinitro-ortho-cresol. Report of eight
fatal cases occurring in Great Britain. Bidstrup,
P.L. & Payne, D.J.H. (1951) Brit. med. J. ii, 16. .. 5
- Poisoning by Dinitro-ortho-cresol. Some observations
on the Effects of Dinitro-ortho-cresol administered by
Mouth to Human Volunteers. Harvey, D.G., Bidstrup,
P.L. & Bonnell, J.A.L. (1951) Brit. med. J. ii, 13. .. 6
- Prevention of acute Dinitro-ortho-cresol (DNOC) Poisoning.
Bidstrup, P.L., Bonnell, J.A.L. & Harvey, D.G. (1952)
Lancet, i, 794. 7
- Poisoning by organic Phosphorus Insecticides. Bidstrup,
P.L. (1950) Brit. med. J. ii, 548. 8

Paralysis following Poisoning by a new organic Phosphorus Insecticide (Mipafox). Report on two Cases. Bidstrup, P.L., Bonnell, J.A. & Beckett, A.G. (1953) Brit. med. J. i, 1068. 9

Anticholinesterases. Paralysis in Man following Poisoning by Cholinesterase Inhibitors. Bidstrup, P.L. & Bonnell, J.A. (1954) Chem. & Industr. 674. 10

Discussion on Agricultural Poisons. Clinical Aspects of Poisoning by organic Phosphorus Insecticides. Bidstrup, P.L. (1952) Clinical Aspects of Poisoning by Dinitro-ortho-cresol. Bidstrup, P.L. (1952) Proc. roy. Soc. Med. 45, 572 & 574. 11

Miscellaneous Subjects

Chronic Mercury Poisoning in Men repairing Direct-current Meters. Bidstrup, P.L., Bonnell, J.A., Harvey, D.G. & Locket, S. (1951) Lancet, ii, 856. 12

Toxicology: 2. Industrial Poisoning. Bidstrup, P.L. (1952) Brit. Ency. med. Practice Interim Suppl. 99. .. 13

Toxicology: Industrial Poisoning. Hunter, D. & Bidstrup, P.L. (1952) Brit. Ency. med. Pract. 12, 2nd Edn. .. 14