CLINICAL PATHOLOGY IN GENERAL PRACTICE

LABORATORY INVESTIGATIONS IN SUSPECTED INDUSTRIAL POISONING

BY

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There are two situations in which a general practitioner may need the help of the laboratory in dealing with patients he suspects to be suffering from industrial poisoning: (1) When the history and clinical picture point to industrial poisoning but he has no direct evidence of such exposure, nor of its magnitude; here both doctor and patient may be unaware of any danger in the patient's work, and a laboratory investigation may be the only way of establishing that exposure has occurred. (2) When the doctor is supervising (as an industrial medical officer) the health of a group of work-people; here the fact of their exposure is known to him, but laboratory tests are required to estimate its degree and identify individuals who are running into danger.

Only a few industrial poisons give rise to specific laboratory findings. The toxic metals can be detected in the body fluids, and carbon monoxide gives rise to a characteristic change in the haemoglobin. Investigations of this nature require not so much an experienced biochemist as a biochemist experienced in the particular technique, as well as a laboratory set aside for the work (the determination of lead in biological fluids provides a good example). These conditions can rarely be fulfilled in general hospital laboratories. In consequence it has been the practice in some regions to attempt to concentrate work of this nature in one or two special laboratories. Unless special facilities of this type are available results may be inaccurate, and it cannot be too strongly emphasized that incorrect results are worse than no results at all. The clinician, therefore, should explore the facilities available to him before requesting unusual investigations to assist him in diagnosis.

The more important use of laboratory investigations in those exposed to industrial poisons lies in prevention. Unfortunately, this work does not fall within the ambit of laboratories associated with the National Health Service, and the practitioner requiring these examinations will have to make special arrangements. Large firms usually establish a laboratory to deal with their own particular health problems, but difficulty arises where the numbers of workmen involved make such provision uneconomical.

It is often possible for the research biochemist to devise tests which will enable a check to be kept on workers exposed to particular poisons. But the methods to be used and the interpretation of results in the prophylactic field raise special problems, and general practitioners wishing to institute this type of routine supervision would be well advised to seek the advice of an expert in industrial medicine.

Whether the laboratory test is to be used for diagnostic or prophylactic purposes it must be carried out with due care, and this may involve much labour in the laboratory. Equal care is necessary, however, in

the collection of specimens, and the practitioner would be wise to consult the laboratory about their tests and the times at which unusual specimens should be submitted.

Details of some of the industrial poisons giving rise to specific changes are briefly discussed below.

Lead-Poisoning

Lead-poisoning still continues to occur and the diagnosis is often missed. Help can be obtained from laboratory investigations provided these have been carried out in a suitable laboratory. In detecting minute quantities of lead in body fluids the biochemist has to take the greatest care: reagents must be "delead" and special glassware used. The latter is prepared by washing with pure hydrochloric acid and rinsing with water twice distilled from all-"pyrex" apparatus. All these time-consuming precautions in the laboratory, however, are of no avail if proper care has not been observed in the collection of samples by the practitioner.

Lead in Urine.—A true and uncontaminated 24-hour sample would theoretically be most suitable, but in practice the collection of spot samples of at least 200 ml. is to be preferred. The urine should be passed direct into all-glass stoppered pyrex flasks (with or without the use of a pyrex funnel). Great care must be taken to avoid contamination of the specimen from lead on the clothing. To avoid the addition of trace metals *no* preservatives must be added. The normal lead content of urine ranges up to 100 µg. per litre. Values in excess of this are found in nearly all lead-workers and no particular level can be taken as indicating poisoning. Raised urinary excretion of lead merely indicates raised absorption and confirms what may be already known, that the patient is a lead-worker. Low-grade absorption will give a urinary figure of up to 150 µg. per litre and suggests good working conditions. Repeated values of 200 µg. indicate substantial absorption. If values are frequently found above 300 µg. absorption is excessive and poisoning may occur at any time. There is considerable daily variation in urinary lead output and reliance should not be placed on single observations. In the supervision of lead-workers the importance of group trends cannot be overemphasized. A high lead level in urine in an individual does not indicate poisoning, nor does a low one completely rule it out. Diagnosis must rest upon the clinical picture taken in conjunction with all laboratory findings.

Lead in Faeces.—This investigation has no place in the detection of individual cases of industrial lead-poisoning and is of little value in assessing an industrial hazard.

Lead in Blood.—This determination has been widely used in the United States. Ten millilitres of blood should be collected in a dry all-glass syringe, cleaned as described above, with a stainless steel needle. The blood should be transferred to a similarly cleaned test-tube and allowed to clot. The normal range of values is 0–80 µg. per 100 ml. of blood.

Coproporphyrin in Urine.—While urinary coproporphyrin concentration is a useful index of the lead hazard in groups of lead-workers in industry, the excretion of this substance is also raised in a number of other diseases and the test has little diagnostic importance.

Blood Examination

While by no means entirely specific, blood examination for punctate basophilia offers a useful test for certain types of lead absorption (not lead tetraethyl). Blood for this purpose is most easily obtained from the lobe of the ear. Films should be spread on thin glass slides (to facilitate the use of dark-ground technique in the laboratory). The film should be thin—in a person not markedly anaemic the spreading slide should be at an angle not greater than 20 degrees. It is easier to judge the quality of the film if the slide lies on a white background—a piece of white blotting-paper is very suitable. Several films should be prepared and these should be allowed to dry in air.

Results must be interpreted with care. Actual counts will depend on factors such as the stain used and the experience of the technician. Many laboratory workers content themselves with reporting "punctates per field"; others use even more cryptic remarks such as "numerous." In the absence of other disease likely to produce this condition (pernicious anaemia, malignant disease) punctate basophilia suggests lead absorption. It is observed in minor degrees in most lead-workers, but large numbers of stippled cells—three or four per field, especially if the granules are large—suggest excessive absorption and the possibility of poisoning. Associated with a haemoglobin estimation, and a limited number of lead-in-urine determinations, this method provides a cheap and objective method of supervising lead-workers.

Mercury

The level of mercury in the urine gives a useful indication of the quantity being absorbed. The collection of the specimen is carried out with the same precautions as for lead.

The normal range of urinary mercury is up to 80 $\mu\text{g.}$ per litre and values in excess of 100 $\mu\text{g.}$ are abnormal. Very high values are often found in those exposed to metallic mercury; for instance, values exceeding 1,000 $\mu\text{g.}$ have been found in such a group of workers, and in isolated cases values exceeded 2,000 $\mu\text{g.}$ These men were all at work, but many showed the rather indefinite clinical picture associated with chronic mercury poisoning. Symptoms should be looked for when the value persistently exceeds 300 $\mu\text{g.}$ per litre.

Arsenic

The patient should be sent to the laboratory so that a fresh specimen of urine can be obtained for examination by the molybdenum-blue colour method. Normal urinary arsenic has been given as 170 $\mu\text{g.}$ of arsenious anhydride per litre.

Carbon Monoxide

Carbon monoxide is one of the commoner poisons, both in industry and in the home, and its detection in the blood is often important for medico-legal purposes. The percentage of carboxyhaemoglobin can readily be measured in the laboratory either by the use of reversion spectroscopy or by the sensitive palladium-ammonium molybdate method.

Ten millilitres of blood should be collected with a sterile dry syringe and oxalate.* The blood should be transferred under paraffin to a test-tube and more paraffin should be added to fill the tube, which should be securely corked. Shaking should be avoided, the tube wrapped to exclude light, and the specimen taken to the laboratory without delay so that the analysis can be carried out as soon as possible.

The blood takes up carbon monoxide very readily and minor quantities are not noticed. For instance, the blood may contain as much as 5% carboxyhaemoglobin after

*The oxalate anticoagulant should preferably be Heller and Paul's solution, which is prepared from 1.2 g. of ammonium oxalate, 0.8 g. of potassium oxalate, and 1 ml. of 40% formaldehyde, the solution being made up to 100 ml. with water: 1 ml. of this solution is suitable for 10 ml. of blood.

smoking cigarettes. In a healthy person *at rest* concentrations up to 15–20% may remain undetected. When the carboxyhaemoglobin reaches 30% a throbbing headache and dizziness are likely to appear, at 50–60% the patient becomes unconscious. If 80% of the haemoglobin is combined with carbon monoxide death occurs rapidly.

Aromatic Amino- and Nitro-Compounds

Aniline, nitrobenzene, and related aromatic compounds give rise to the formation of abnormal haemoglobin derivatives in blood. The erythrocytes of patients who are cyanosed may contain sulphaemoglobin and methaemoglobin, and methaemalbumin may be present in the plasma.

To examine for these, 10 ml. of blood should be withdrawn by syringe and transferred to a tube, where it must be preserved with a mixture of sodium fluoride and thymol,† which acts as a preservative and anticoagulant. Air should be excluded by filling to the stopper with liquid paraffin and the estimation should be made as soon as possible. Sodium citrate should not be used as an anticoagulant as it interferes with the methaemoglobin determination.

Probably about 1% of the total haemoglobin in the red blood cells is normally present as methaemoglobin. It is only when the methaemoglobin concentration reaches levels of approximately 40% that dyspnoea occurs on exertion, although obvious cyanosis may be present at much lower levels. The cyanosis from methaemoglobin clears in a day or two, but that resulting from sulphaemoglobin may persist for several weeks.

Trinitrotoluene

Workers exposed to trinitrotoluene excrete metabolites in the urine which give a positive Webster test. This consists in adding alcoholic potash to an ethereal extract of the acidified urine, when a violet colour appears. This test is of value only in demonstrating—what is usually well-known—that the patient is working with T.N.T.

Benzene

Blood changes following benzene absorption are important but not specific. Leukopenia, anaemia, or even leukaemia may be observed.

New Chemicals

New chemicals are continually being developed for use in industry. When there is any suspicion of their being poisonous it is one of the duties of the research biochemist to devise methods for their detection and estimation in body fluids. If this is impossible he should attempt to devise an indirect method for assessing the degree of intoxication. Some of the newer chemicals used in agriculture illustrate this.

Selective Weedkillers

Dinitro-*ortho*-cresol (D.N.O.C.), which is used as a selective weedkiller, gives rise to poisoning in man. The clinical picture in mild cases is not clear cut, though help in diagnosis can be obtained from the estimation of this substance in the blood. This is a comparatively simple procedure and can be carried out on small samples of blood. It is particularly useful in supervising the health of those whose work involves exposure to the poison.

The practitioner should submit a sample of 2 ml. of blood to the laboratory. This allows of duplicate tests. The sample is best withdrawn from a vein and must *not* be allowed to clot. A 2-ml. syringe with a fine hypodermic needle serves well. The best anticoagulant is heparin, and suitably prepared tubes can usually be obtained from the laboratory. If such a prepared tube is not available, any clean dry tube may be used; clotting should then be prevented by the previous addition of a few crystals of sodium

†One gramme of sodium fluoride mixed with 0.1 g. of thymol crystals: 0.1 g. of this mixture is taken for 10 ml. of blood.

citrate. Accidental contamination of the sample by chemicals on the skin must be carefully avoided by thorough cleansing of the site of venepuncture with spirit. In order to avoid false peak values, samples should *not* be taken within eight hours of the patient's last exposure. It is not necessary to add any preservative, as D.N.O.C. determinations can readily be carried out on whole blood which is over a week old.

Normal values are usually supplied by the laboratory doing the test. Since D.N.O.C. is a cumulative poison and is only slowly excreted, Bidstrup and her colleagues* recommended that a man should be removed from further contact for at least six weeks, if the blood level, eight hours after his last exposure, is 20 µg. per g. or higher.

Organic Phosphorus Insecticides

The organic phosphorus insecticides are now being widely used all over the world. These substances are toxic to man and produce their effects by inhibiting cholinesterase. In order to detect excessive absorption in workmen using these insecticides, it is necessary to estimate the quantity of this enzyme in the blood. This is not a simple procedure but arrangements have been made for it to be carried out in certain National Health Service Laboratories in *suspected cases of poisoning*.†

There are micro-methods for this determination, but the practitioner would be wise (unless advised to the contrary by his laboratory) to submit a blood sample of at least 2 ml. and preferably 5 ml. Should a micro-method be in use and the practitioner be advised to submit small samples such as can be obtained from a finger prick, it is most important to see that the site is adequately cleaned before pricking, since traces of the insecticide in the sample lead to false low cholinesterase readings. Clotting should be prevented by the use of a heparinized tube or sodium citrate (as for D.N.O.C.); oxalate should not be used. No preservative is required, as enzyme activity of the blood is unimpaired even after a few weeks.

In the absence of an agreed international unit of cholinesterase activity, the amount of enzyme is expressed as a "number."‡ The normal range in healthy adults for whole blood is 80–130 units. Signs of systemic poisoning occur when this figure drops to 20–30 units, though a few patients have shown symptoms when the "number" was in the normal range. The results will almost certainly be interpreted for the practitioner by the laboratory according to the scale in use locally.

The greatest value of this test lies in prevention. In this work the wide range in the normal makes it advisable to have pre-employment determinations carried out on men who are about to be exposed to this poison, and they should subsequently be tested at weekly intervals. A marked fall in a man's cholinesterase number should be regarded as a danger sign and he should be removed from further exposure until his enzyme activity has returned to normal. This recovery is not rapid and may well take six to eight weeks.

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*Bidstrup, P. L., Bonnell, J. A. L., and Harvey, D. G. (1952). *Lancet*, **1**, 794.

†Dr. E. N. Allott, Group Laboratory, Lewisham Hospital, London, S.E.13; Dr. D. H. Fulton, Department of Pathology, Memorial Hospital, Peterborough; Dr. E. M. Darmady, Central Laboratory, Milton Road, Portsmouth; Dr. P. Kidd, Department of Pathology, Royal Infirmary, Worcester.

‡Aldridge, W. N., and Davies, D. R. (1952). *British Medical Journal*, **1**, 945.

Reports of Societies

THE CRIMINAL AND THE DOCTOR

The contemporary crowding of our prisons and the frequency with which young men and women are turning to crime for a living have shocked modern society. Lately, also, the publicity accorded to cases of homosexuality and other sexual offences has heightened the demand that vigorous steps should be taken to mend matters. Unfortunately, no two people agree about what should be done. The psychiatrist has one remedy, the police another, and utterances on the subject from the Bench are conflicting. All are agreed, however, on two things: the urgency of reclaiming all those who can be saved from a life of crime, and the need to protect society from those who cannot.

It is against this background that the International Society of Criminology, with the help of Unesco and the British Council, arranged a two-weeks course in London on "Recent Advances in the Study and Treatment of Offenders." The course ran from March 24 to April 13, and brought together lawyers, magistrates, doctors, psychiatrists, police, prison administrators, sociologists, and other interested people. It consisted of lectures and discussions, and visits to prisons, Borstals, approved schools, and other institutions. The course was directed by Dr. DENIS CARROLL, president of the International Society of Criminology, and Dr. HERMANN MANNHEIM, reader in criminology at London University. Below are reported four of the medical contributions. They deal with electroencephalographic studies, hormone treatment of sex offenders, psychotherapy in prison, and "typological" research on adolescents sent to Borstal institutions.

Electroencephalographic Studies

Speaking on "Electroencephalographic Studies of Offenders," Dr. DENIS HILL (senior lecturer in clinical neurophysiology, Institute of Psychiatry, London University) gave a general survey of work in this field. While the electrical patterns found in epilepsy, brain tumour, and other structural brain disorders were different in kind from the normal record, 10% of the general population showed minor differences in degree, and the study of these was only just beginning. These "variant" records did not indicate any gross structural abnormality, and would be considered normal for children or adolescents in whom, under experimental conditions, they could be produced occasionally by emotional frustration. As the personality trait most often accompanying these aberrant records was undue aggressiveness, it was reasonable to suppose they indicated some failure of the brain to mature and reach integrated functioning, with a resulting imbalance and lack of emotional control. Individuals showing such patterns were more susceptible to physiological stresses, such as a low blood sugar, oxygen lack, and alcohol, and they were also less able to tolerate emotional frustration.

Turning to studies of offenders, Dr. Hill emphasized that no connexion could be found between the E.E.G. tracing and antisocial behaviour as such. Nevertheless, in a recent study of young delinquents, only 16% showed normal recordings. In the prison population, 80% of psychopathic personalities showed variant recordings, a similar proportion to psychopaths in mental hospitals, but among the remainder of the prisoners variant recordings were also abnormally frequent, and these variant patterns were related to aggressiveness. Studies of murderers had been negative in those cases where killing was incidental to another offence, but in those cases where there appeared to be no motive, or where the motive was trivial, three-quarters showed variant records, a fact which indicated the need for close investigation in such cases. There was also a surprisingly high incidence of epilepsy among the