for study of the animals, without necessity for immunosuppressive therapy. Halothane anaesthesia was effective; the animals were kept fairly light throughout the procedure and were usually on their feet within a few hours of the operation. In those animals surviving more than a week classical liver failure did not appear to be the cause of death. However, the gastrointestinal haemorrhage may well have been due to inadequate liver function, though the exact mechanism has not been determined. It will certainly be of interest to study the gastric secretion, metabolism of histamine, the haemodynamics of portal venous flow, and the composition and distribution of bile in these animals. Peptic ulceration is a common complication of orthotopic liver transplantation in dogs. The Bristol workers have also observed gastrointestinal haemorrhage in pigs with orthotopic liver transplants and have demonstrated superficial mucosal erosions in the cardiac portion of the stomach. A perforated duodenal ulcer was the cause of death of one of the pigs in the French experiments.

In our pig herd skin grafts are rejected aggressively when the donor and recipient are unrelated (Binns, 1967), and even in littermates rejection is the rule, though skin grafts may persist up to three weeks. The mechanism of acceptance of an orthotopic liver transplant in our longest-surviving animal at seven months and a similar animal of the Bristol group at nine months (Peacock, personal communication) has not been determined. Though splenectomy has little effect on the survival time of transplanted tissue in most species that have been studied, it is possible that splenectomy in pigs with liver transplants may influence the outcome of the transplant.

This early experience encourages us to pursue further studies with liver transplantation in the pig.

Summary

Our preliminary experience with orthotopic liver transplantation in the pig is reported. Of the 19 operations performed 13 animals survived the procedure and six lived for a week or more. One pig with an orthotopic liver transplant from a littermate lived for seven months after operation without any immunosuppressive therapy and died from intestinal obstruction, with minimal microscopical evidence of liver damage.

We wish to thank Dr. Marek Zakiewicz for the help he has given with the anaesthesia of the pigs, and we acknowledge the excellent technical assistance that we have received from the staff of the Department of Surgery, University of Cambridge, and the Agricultural Research Council at Babraham. We are most grateful to Dr. R. D. Keynes for providing facilities at the A.R.C., Babraham.

REFERENCES

- Binns, R. M. (1967). *Nature (Lond.)*, **214**, 179.
 Cordier, G., Garnier, H., and Clot, J.-P. (1966). *Mém. Acad. Chir.*, **92**, 799.
 Garnier, H., *et al.* (1965). *C.R. Acad. Sci. Paris*, **260**, 5621.
 Moore, F. D., *et al.* (1960). *Ann. Surg.*, **152**, 374.
 Staryl, T. E., Kaup, H. A., jun., Brock, D. R., Lazarus, R. E., and Johnson, R. V. (1960). *Surg. Gynec. Obstet.*, **111**, 733.
 Terblanche, J., *et al.* (1967). *Brit. J. Surg.*, **54**, 231.

Lead Absorption in Children

NEIL GORDON,* M.D., F.R.C.P.ED., M.R.C.P.; E. KING,* R. I. MACKAY,* M.B., CH.B., M.R.C.P., D.C.H.

Brit. med. J., 1967, **2**, 480-482

The possibility of a causal relationship between lead absorption and mental retardation has been suggested by Moncrieff *et al.* (1964). They claimed that lead was a greater factor in producing mental retardation than previously thought and that the estimation of lead in the blood was the only certain way of demonstrating excessive exposure to lead. It was believed that a blood lead level of over 36 $\mu\text{g.}/100\text{ ml.}$ was an indication of intoxication, because 80 normal children were examined and all but two had levels below this. This problem has been studied in Manchester and Salford, a densely populated area undergoing an extensive slum-clearance programme.

Clinical Material

In order to try to establish the possible role of lead poisoning the blood lead levels of 147 mentally retarded children aged 5 months to 18 years were examined. They were either attending training centres under the authority of the Salford Mental Health Department or had been admitted for investigation to the wards of the Royal Manchester Children's Hospital and the paediatric department at Hope Hospital, Salford. A control group of 73 children aged 1 to 19 years were taken from those admitted to the wards of these hospitals for known conditions that precluded the possibility of lead poisoning. There are obvious

disadvantages of choosing such children suffering from a variety of medical and surgical diseases, but there was no possibility of collecting a sufficiently large number in normal health. The controls were drawn from the same population as the mentally handicapped children but were not matched for race or social class. The children with Down's syndrome were analysed separately from the other mentally handicapped children to see if the blood leads of a group with a known aetiology differed significantly from the rest. The blood lead level of 50 $\mu\text{g.}/100\text{ ml.}$ was chosen as the possible dividing line between normality and abnormality on the previous experience of the Nuffield Department of Occupational Health in the area of Manchester and Salford. The blood lead estimations were repeated on 14 of the children with levels of over 50 $\mu\text{g.}/100\text{ ml.}$

Of the whole group of mentally handicapped children there were 121 with blood lead levels below 50 $\mu\text{g.}/100\text{ ml.}$ and 26 above this figure. Among these were 24 mongol children, and the comparable values for them were 19 and 5 respectively. The control group showed 60 children with blood lead levels below and 13 with levels above 50 $\mu\text{g.}/100\text{ ml.}$ The 14 children whose blood lead levels were re-examined included eight of the group of mentally handicapped of uncertain cause, two of the mongols, and four of the controls. In 10 of them the blood lead level had returned to a value below 50 $\mu\text{g.}/100\text{ ml.}$ One of each of the first two groups and two of the controls still had a level of above 50 $\mu\text{g.}/100\text{ ml.}$ on the second examination.

* The Service for the Handicapped Child, Royal Manchester Children's Hospital and the Nuffield Department of Occupational Health, Manchester University.

Statistical analyses of the results in the three groups of mentally handicapped children of uncertain aetiology, mongol children, and controls gave the results shown in the Table. The data indicate that the three groups do not differ significantly as regards blood lead levels.

The blood lead was estimated by the method used by the Department of Industrial Medicine (Medical Research Council) modified to use 3 ml. of blood (King and Thompson, 1961; Moncrieff *et al.*, 1964).

Statistical Analyses of Results

Group	No. in Group	Mean	S.D.	T (Correlation Between Blood Lead Level and Age of Patient)
Mentally handicapped ..	123	31.6 $\mu\text{g./100 ml.}$	17.7	0.224
Mongols ..	24	35.1 $\mu\text{g./100 ml.}$	16.2	0.040
Controls ..	73	30.9 $\mu\text{g./100 ml.}$	20.9	0.141

Discussion

The three groups do not differ significantly as regards blood lead levels, which strongly suggests that within the limits of this study there is no evidence that lead intoxication is playing a significant part in the aetiology of the mental retardation. The findings among the children with Down's syndrome do not indicate that, even if lead intoxication is not of aetiological significance, these particular children are more at risk from the ingestion of lead than the controls. Byers (1959) regarded values of 60 $\mu\text{g./100 ml.}$ or over as pathological, though drawing attention to the fact that a single determination of lead in the blood in normal individuals may be temporarily above levels generally regarded as toxic. In this study the scatter of blood lead levels is as marked among the controls as the mentally retarded (Figs. 1, 2, and 3), and from the analysis

FIG. 1.—Levels of lead in blood of mentally handicapped children of uncertain aetiology.

of these figures there is no clear-cut blood lead level which can be designated as normal. There is a possibility of a weak association of the blood lead level with age in the group of mentally retarded children, but this does not seem strong enough to implicate duration of exposures as a definite factor.

The main problem is whether the finding of a random value above an accepted level of normal for blood lead among the general population is of significance. The frequency with which the level returns to normal when the test is repeated among these children suggests that this may not be so. Obviously such a finding raises the possibility that the child is being exposed to lead intoxication, but the results of a random test should be interpreted with caution. The test should be repeated to check the findings, and a mobilization test may be a method of differentiating the child who is truly suffering from lead poisoning from the one who has been exposed to a temporary contamination of his food. The edathamil calcium disodium diagnostic test can differentiate

between normal individuals and those with increased exposure to lead. Whitaker *et al.* (1962) showed that the average excretion of lead in the urine in the 24 hours after administration of the drug was 165 $\mu\text{g./l.}$ in normal children, 995 $\mu\text{g./l.}$ in those with suspected lead poisoning, and 1,966 $\mu\text{g./l.}$ in those with classic lead poisoning.

FIG. 2.—Levels of lead in blood of mongol children.

FIG. 3.—Levels of lead in blood of control group of children.

“Normal” values of blood lead are known to vary from rural to urban surroundings, owing to opportunities for absorbing lead. Chisholm (1965) has stressed that blood lead measurements require careful interpretation and that several assessments are necessary to ascertain trends. He lists the following factors which may be of significance: the haematocrit, intercurrent infections, coincident bone disease, current or recent administration of chelating agents, current or recent excessive absorption of lead, and the time interval since excessive absorption ceased. Sometimes the treatment with chelating agents of a child, mentally retarded from a known cause, who may have been accidentally poisoned by lead has to be considered. Moncrieff *et al.* (1964) mentioned such a child with a blood lead level of 48 $\mu\text{g./100 ml.}$ who improved on treatment, but variations in behaviour are such a characteristic of the type of child under consideration that clinical criteria would not seem sufficient on their own.

Increased attention, hospitalization, and a number of other factors may influence the behaviour of a mentally handicapped child. Therefore, unless the diagnosis of lead intoxication can be established with reasonable certainty—for instance, by finding an excretion of lead in the urine of more than 500 $\mu\text{g./l.}$ in the 24 hours after a test dose of edathamil calcium disodium—the justification for treating a large number of children with ethylene diamine tetra-acetic acid (E.D.T.A.) or penicillamine seems questionable. In view of the possible nephrotoxic effects of E.D.T.A. and penicillamine and their chelates, the risks of treatment for the individual patient must be weighed against the possible advantages.

Summary

It has been claimed that a raised blood lead level is a common finding among mentally retarded children and that this is of aetiological significance. One hundred and twenty-three mentally handicapped children of uncertain aetiology, 24 with mongolism, and 73 controls have been examined for lead intoxication. The results indicate that the three groups do not differ significantly as regards blood lead levels and no definite evidence of either acute or chronic lead poisoning has been obtained.

This study does not suggest that these mentally backward children have been particularly at risk from lead poisoning, and emphasizes the limited value of an isolated estimation of the blood lead level. These conclusions do not depend on whether 36 or 50 μ g. of lead per 100 ml. of blood is regarded as the upper limit of normal. However, if a value is found which

is above the accepted level for the population in a particular area, this is an indication for further investigation, but not necessarily for treatment.

We wish to express our thanks to Mrs. J. H. Kellgren for all the time and effort she gave to collecting the data on the patients in this study.

REFERENCES

- Byers, R. K. (1959). *Pediatrics*, 23, 585.
 Chisolm, J. J., jun. (1965). *Develop. Med. child Neurol.*, 7, 529.
 King, E., and Thompson, A. R. (1961). *Ann. occup. Hyg.*, 3, 247.
 Moncrieff, A. A., Koumides, O. P., Clayton, B. E., Patrick, A. D., Renwick, A. G. C., and Roberts, G. E. (1964). *Arch. Dis. Childh.*, 39, 1.
 Whitaker, J. A., Austin, W., and Nelson, J. D. (1962). *Pediatrics*, 29, 384.

Heparin Administration by Constant Infusion Pump

ANTHONY J. HANDLEY,* M.B., B.S.

Brit. med. J., 1967, 2, 482-484

This paper presents a method for the continuous intravenous infusion of heparin by means of a syringe-pump, and compares it with the technique of intravenous drip infusion (Harden, 1963).

Methods

The syringe-pump used was that described by Pegg *et al.* (1963). It consists of a small constant-speed mains electric motor which rotates a screw thread. This in its turn drives home the plunger of a standard glass syringe (see illustration¹).

Syringe-pump connected to a patient.

The pump is regulated to give a steady infusion of 20 ml. in 12 hours. Two anaesthesia extension sets (Baxter model R33), each 12 in. (30 cm.) long, are used to connect the syringe to the patient. Both the syringe and the extension sets are filled with heparin solution of the required strength.

A suitable forearm vein is selected, and a Portex 12-in. (30-cm.) nylon intravenous cannula size 16 with terminal Luer fitting inserted by means of an introducing needle as described by Macgregor (1960). The arm requires little or no splinting, and the length of extension tubing used allows the patient considerable movement.

The following assessment of this technique and the drip-infusion technique of Harden (1963) was made.

Results

Twenty-four patients suffering from thromboembolic disease were treated with heparin: 18 were given it by pump infusion and six by drip infusion. The degree of anticoagulation produced was measured by the whole-blood clotting-time, a modification of the Lee and White (1913) method being used. Venous blood was taken from the arm not used for the heparin infusion.

The mean clotting-time of the 24 patients before starting heparin was 4.8 minutes, with a range of 3.5 to 6.5 minutes. The mean clotting-time of 12 normal controls by the same method was 4.75 minutes, with a range of 3.5 to 5.5 minutes.

Pump Infusion.—Of the first 12 patients treated by pump infusion, 10 were given 20,000 units of heparin over each 12-hour period that the syringe pump ran. One patient (Case 1) was given 24,000 units and one (Case 9) was given 7,000 units over each 12-hour period. The average length of treatment was 7.3 days, with a range of 1 to 14 days. During heparin therapy six random clotting-times were estimated for each patient, spread out so far as was possible over the whole period of treatment. The results are shown in Table I. Of the patients receiving 20,000 units of heparin in 12 hours, only two (Cases 10 and 11) had a mean clotting-time outside the range of 2.4 to 3.5 times their normal (pre-heparin) times. This probably represents optimum anticoagulation (Duff *et al.*, 1951; Wood, 1956; Carey and Williams, 1960; Griffith and Boggs, 1964; Brigden, 1966). The mean clotting-time in Case 1 was 4.2 times normal, and in Case 9 it was 2.3 times normal.

Loading-dose.—The effect of an initial "loading-dose" of heparin was studied in six further patients; three were given 5,000 units of heparin intravenously at the time the syringe-pump was started, and three were given no such loading-dose. Clotting-times were measured before treatment, at half-hour and two hours after the pump was started, and on two further random occasions. The results are shown in Table II. All the patients eventually achieved satisfactory clotting-times. In the three receiving no loading-dose of heparin the clotting-times at half an hour were uniformly unsatisfactory (less than twice normal) and at two hours one (Case 18) was unsatisfactory and one (Case 17) barely satisfactory. In the three patients receiving the 5,000 units initial loading-dose, the half-hour and two-hour clotting-times were all very near the final clotting-times achieved.

* House-physician, Westminster Hospital, London S.W.1. Present address: The London Hospital, Whitechapel, London E.1.

¹ The pump described was made in the Physics Department, Westminster Hospital. Syringe-pumps of various designs are available commercially, and a list of known suppliers will be furnished on request to the author.