qualone for, without such information, readers cannot determine whether dialysis is in fact of any value in this form of poisoning? [1] Indeed, apart from circumstantial evidence, notoriously unreliable, there is nothing to indicate that the patient had ingested mandrax.

Regional Poisoning Treatment Centre,
Ward 3, The Royal Infirmary,
Edinburgh 3.

HENRY MATTHEW.

EVALUATING DRUG TRIALS UNSEEN

SIR,—Doctors whose responsibility it is to advise the pharmaceutical manufacturer on evaluation of new remedies will find themselves in general agreement with your note on the subject last week (p. 109), but some rather important qualifications have been omitted.

The double-blind trial is not itself a passport to success in drug evaluation, and in the investigation of new remedies for symptomatic therapy the double-blind trial is often inappropriate. As Cromie [2] has stressed, subjective assessment of subjective symptoms should not be scorned. Control of all the variables of weight, age, and sex of the patient leave out of consideration the vital question of the patient's personality, and, equally important, the attitude of the doctor to his patient and towards the new medicine.[3] Bradford Hill reminded us some years ago that the mere use of tests of statistical significance did not ensure that the conclusions reached were correct, and that, if the data were not comparably valid, statistical tests were valueless.[4]

Controlled trials, statistical significance, and random allocation of treatments have a place in drug evaluation, provided the trial itself is very carefully planned. The computer is surely destined to play a major role in the future practice of medicine, but it will be a sad day if careful clinical observation is replaced by a string of mathematical symbols.

The Bayer Products Co.,
Surbiton-upon-Thames,
Surrey.

J. M. MUNGAVIN.

FATAL 'LOMOTIL' POISONING

SIR,—The ever-growing list of proprietary medications which are made available to the medical practitioner provide him with a complex and often poorly understood therapeutic armament. The dangers of accidental poisoning with such drugs as salicylates or barbiturates are now well recognised; this is not the case, however, for many of the newer, widely used preparations which may often contain a combination of two or more drugs.

We briefly report here the death of a 2-year-old boy after the accidental ingestion of 'Lomotil' tablets (each tablet contains 2·5 mg. of diphenoxylate hydrochloride and 0·025 mg. of atropine sulphate). For the treatment of a mild diarrhœal illness lomotil liquid had been prescribed for the patient and lomotil tablets for his mother. 6 hours after accidental ingestion of twelve tablets the patient had been found to be grunting with mild respiratory distress, and this had rapidly progressed during the next 2 hours; respiratory and cardiac arrest had occurred on arrival at a local casualty department and, despite the prompt institution of external cardiac massage, mechanical ventilation, and nalorphine injections, cardiac arrest persisted for 50 minutes.

On transfer to this hospital, 12 hours after ingesting the tablets, the patient was hypothermic (temperature 89° F [32°C]), deeply unconscious with fixed dilated pupils, hypotonic, unresponsive to painful stimuli, and in peripheral circulatory failure; the heart-rate was 120 per minute and the blood-pressure unrecordable. An electroencephalogram (Dr. G. Pampiglione) showed practically compiete equipotentiality for cerebral signal either spontaneously or in response to various stimuli; these features suggested unrecoverable cerebral function. Supportive therapy and nalorphine injections were continued, but these measures did not result in clinical improvement, and serial electroencephalograms remained unchanged. *Shigella sonnei* was cultured from the diarrhœal stools. He died 65 hours after admission; necropsy showed gross cerebral œdema.

The pharmacological action of atropine is well documented, and the total ingested dose in this child was well below toxic amounts. Diphenoxylate hydrochloride is somewhat similar to pethidine in its chemical structure but its metabolism is poorly understood; in our patient it is probable that this drug caused respiratory depression which could not be reversed and ultimately proved fatal. Although respiratory depression is listed amongst the effects of overdosage of lomotil, it seems likely that the dangers are insufficiently known, since the drug is widely prescribed for what is often a mild self-limiting disorder. Indeed, in a double-blind study of 50 children with diarrhœa, Harris and Beveridge [1] found no clear pattern to suggest that lomotil influences the course of the condition.

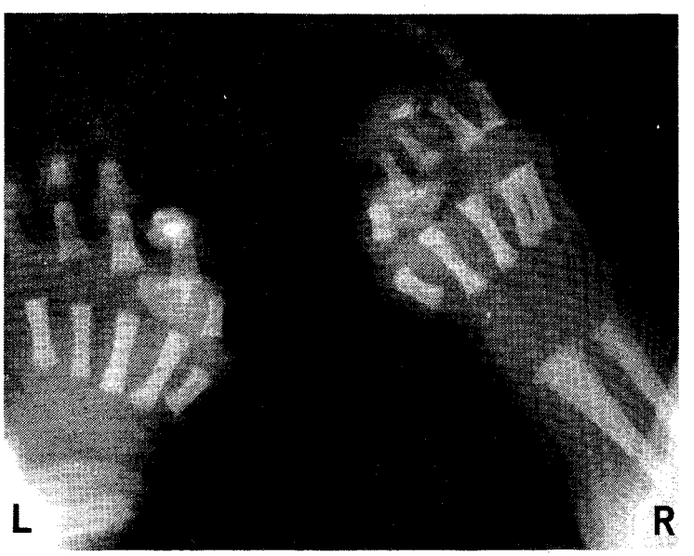
We thank Prof. O. Wolff for his permission to report this patient.

Hospital for Sick Children,
Great Ormond Street,
London W.C.1.

JOHN T. HARRIES
MARY ROSSITER.

LYSERGIDE AND CANNABIS AS POSSIBLE TERATOGENS IN MAN

SIR,—The letter by Dr. Hecht and his colleagues [2] prompts us to describe an infant with a terminal transverse deficit of portions of fingers of the left hand, and syndactyly of the right hand with shortened fingers, whose mother is believed to have been exposed to lysergide and cannabis during pregnancy.



X-ray of left (L) and right (R) hands of affected newborn.

The thumbs project medially. Note absence of several phalangeal bones.

The mother, who had had no previous pregnancies, was 23 years old. The baby, a Caucasian girl, was born, by normal vertex delivery, in June, 1968, 13 days before the expected date of confinement; birth-weight was 5 lb. 3 oz. (2350 g.). The second, third, and fourth fingers of the right hand were webbed and abnormally short. The left hand showed absent nails and shortened fourth and fifth fingers. There was webbing between the second and third toes of the right foot and talipes equinovarus of the left foot. The accompanying figure

1. Proudfoot, A. T., Noble, J., Nimmo, J., Brown, S. S., Cameron, J. C. *Scott. med. J.* 1968, **13**, 232.
2. Cromie, B. W. *Lancet*, 1963, ii, 994.
3. *Br. med. J.* 1961, i, 43.
4. Bradford Hill, A. *Practitioner*, 1963, **190**, 85.

1. Harris, M. J., Beveridge, J. *Med. J. Aust.* 1965, ii, 921.
2. Hecht, F., Beals, R. K., Lees, M. H., Jolly, H., Roberts, P. *Lancet*, 1968, ii, 1087.

shows an X-ray of the hands in the newborn period, demonstrating three phalangeal bones missing in the left hand, and five missing in the right hand.

Chromosome studies of peripheral leucocytes from the baby were done soon after discharge from the hospital. Thirty-one metaphases were examined, and none showed evidence of broken chromosomes. Thirty cells were 46,XX and one was 45,XX,G−.

The similarity between the terminal transverse hand abnormalities in our case and in the patient of Dr. Hecht and his colleagues seems to be worth noting. It should also be pointed out that the fibula and several tarsal, metatarsal, and phalangeal bones were absent in the right lower limb of the infant described by Zellweger et al.[3]

While we must be cautious about assuming a causal relation from such limited data, it is important to keep alert to the possibility of the emergence of a peculiar pattern of defects.

This study was aided by grants AM-02504 and 5-TO-2-CH-1081 from the National Institutes of Health, United States Public Health Service.

Genetic and Endocrine Unit,
Department of Pediatrics,
State University of New York,
Upstate Medical Center,
Syracuse, N.Y. 13210.

GERSON CARAKUSHANSKY
RICHARD L. NEU
LYTT I. GARDNER.

PHENAZOPYRIDINE-HYDROCHLORIDE HÆMOLYSIS

SIR,—Three cases of hæmolysis caused by phenazopyridine hydrochloride ('Pyridium') have been reported in North American medical journals.[4 5] We report here a further case.

An 86-year-old woman, admitted to hospital with pneumonia, was successfully treated with ampicillin. She also complained of long-standing dysuria and nocturia but urinary bacterial culture was negative. She was given pyridium, in the normal dosage of 200 mg. three times a day, with fairly good symptomatic improvement. After a month, she was seen to be clinically jaundiced; her urine contained excess urobilinogen but no bile. The hæmoglobin level, which had been 11 g. per 100 ml. before pyridium therapy, had dropped to 8·2 g. per 100 ml. with a reticulocyte-count of 15·6% and many Heinz bodies. The Coombs test was negative and there was no evidence of congenital hæmolytic disease. The drug was stopped, but the patient required transfusion with packed cells because of the development of heart-failure. Her general condition gradually improved and the reticulocyte-count slowly fell over the next 10 days. The blood-urea level was 80 mg. per 100 ml. and creatinine clearance was 23 ml. per minute.

Pyridium (2,6,-diamino-3-phenylazopyridine hydrochloride) is an azo dye with urinary-tract-analgesic properties, and it is still often used. It is chemically related to phenylhydrazine, which was formerly used to treat polycythæmia. Pyridium causes hæmolysis by a toxic action on red blood-cells, producing methæmoglobinæmia and Heinz-body anæmia. If renal impairment is present, toxic concentrations may be reached, and it may then be a dangerous drug.

Royal South Hants Hospital,
Southampton.

A. J. EISINGER
R. JONES.

NATURAL HISTORY OF AORTIC STENOSIS

SIR,—I read with interest your annotation.[6] One point in the evolution of the disease which is not mentioned in most textbooks of cardiology is that occasionally patients present with classical signs of pure aortic stenosis and in time develop evidence of moderate, but definite, aortic incompetence. I have followed up three such cases, all of them with calcific aortic stenosis. Obviously when the immediate diastolic murmur, at first fairly audible, became prominent and the character of the pulse changed, the suspicion arose of bacterial endocarditis, but no evidence of this was found. All three patients had presented with angina rather than cardiac failure. As aortic incompetence developed they tended to lose their angina and to develop congestive cardiac failure.

The cause of this evolution of the disease is unclear. It may well be that the valves, becoming more heavily calcified, would fail not only to open properly but also to close.

Whittington Hospital,
London N.19.

E. MONTUSCHI.

RENAL TRANSPLANTATION

SIR,—The rather swash-buckling attitude to tissue typing in your annotation (Jan. 4, p. 33) leaves the impression it was meant to convey—that all is well. Tissue typing is about tissue sharing of antigens. The basic evidence purports to show that lymphocytes share tissue antigens with other tissues. The evidence so far produced indicates that the assumption is not in fact true and that some species differences render generalisations difficult. The fact that I [1] showed that dog skin and kidney shared antigens seems only to confuse the picture in man—man can reject skin and yet retain a kidney transplanted from the same donor,[2 3] although leucocyte iso-antigens have been demonstrated on skin epidermal cells by means of immune adherence.[4] I moved on to testing skin and kidney for antigen sharing because I was unable to confirm, in the dog, the report of antigen sharing between rabbit leucocytes and skin.[5] Indeed, the negative results reported by Calne et al.[6] make this point.

The criterion of correlation between grafts and the HL-A system in man was originally mere length of skin-graft survival,[7] but then it was changed to the histopathological features in allotransplanted kidneys,[8] and it has been changed again to the functional state of allotransplanted kidneys.[9] Length of survival has been abandoned clinically because "An immediate improvement in clinical results, however, should not be expected, for the initial mortality is high in both matched and mismatched patients",[9] but previously we were assured that "Leucocyte group antigens play a distinct role in determining the rate and intensity of HL-A responses in man".[10] Longevity comes into the picture now only after a period of one year,[9] and, logically, this implies that factors other than the HL-A system are responsible for early rejection.

Although mere survival has been abandoned the evidence, involving length of survival as proof of the correlation between HL-A and the leucocytes, is still cited.[11] It is this evidence about which I have always been in honest doubt. Ceppellini et al.[7] reported skin-graft survivals with unrelated donors to be 12·1 days, with parents as donors 14·1 days, and with siblings 16·7 days; and with ABO and HL-A compatible siblings 19 days,[12] but Bach and Kisken [13] reported a mean of 26 days. Then, Bach and Amos [14] reported that, in HL-A compatible siblings, the mixed lymphocyte test showed nil transformations

1. Dempster, W. J. *Br. J. plast. Surg.* 1953, **5**, 228.
2. Hamburger, J., Vaysse, J., Crosnier, J., Auvert, J., Lalanne, C. M., Hopper, J. *Presse méd.* 1959, **67**, 1771.
3. Merrill, J. P., Murray, J. E., Harrison, J. H., Friedman, E. A., Dealy, J. B., Dammin, G. J. *New Engl. J. Med.* 1960, **262**, 1251.
4. Melief, C. J. M., Hart, M. van der, Engelfriet, C. P., Eysvoogel, V. P., van Loghem, J. J. *Vox sang.* 1968, **15**, 187.
5. Medawar, P. B. *Br. J. exp. Path.* 1948, **29**, 58.
6. Calne, R. Y., Davis, D. R., Medawar, P. B., Wheeler, J. R. *Transplantation*, 1966, **4**, 742.
7. Ceppellini, R., Curtoni, E. S., Mattivz, P. L., Leigheb, G., Visetti, M., Colombi, A. *Ann. N.Y. Acad. Sci.* 1966, **129**, 421.
8. Van Rood, J. J., van Leevwen, A., Bruning, J. W. *J. clin. Path.* 1967, **20**, suppl. p. 513.
9. Patel, R., Mickey, M. R., Terasaki, P. I. *New Engl. J. Med.* 1968, **279**, 501.
10. Dausset, J., Rapaport, F. T. *Ann. N.Y. Acad. Sci.* 1966, **129**, 408.
11. Batchelor, J. R. *Clin. chim. Acta*, 1968, **22**, 95.
12. Van Rood, J. J., Leevwen, A., Schippers, A., Ceppellini, R., Mattivz, P. L., Curtoni, S. *Ann. N.Y. Acad. Sci.* 1966, **129**, 467.
13. Bach, F. H., Kisken, W. A. *Transplantation*, 1967, **5**, 1046.
14. Bach, F. H., Amos, D. B. *Science, N.Y.* 1967, **156**, 1506.

3. Zellweger, H., McDonald, J. S., Abbo, G. *ibid.* 1967, ii, 1066.
4. Greenberg, M. S., Wong, H. *New Engl. J. Med.* 1964, **271**, 431.
5. Gabor, E. P., Lowenstein, L., de Leeuw, N. K. *Can. med. Ass. J.* 1964, **91**, 756.
6. *Lancet*, 1968, ii, 1334.