to ensure that a certain minimum concentration of penicillin is being obtained, the actual level being unimportant provided it is above the therapeutic one for the organism concerned.

Owing to the possible contamination of the urine, the *Staph. aureus* method is unsuitable for urine penicillin assays and the *Sarcina lutea* method must be used.

Summary and Conclusions

Serum penicillin levels and urine excretion rates were measured in six subjects, using two intramuscular and two oral preparations of penicillin. The two standard methods of assay are described in some detail, and the results obtained with both methods are compared.

The results obtained clearly indicate that oral penicillin is no substitute for parenteral therapy when consistently high levels are required. Where oral therapy is indicated phenoxymethyl penicillin gives adequate and reliable blood levels. Benzathine penicillin appears to give disappointing results in adults, and it is probably of more value in children.

The *Sarcina lutea* assays were performed throughout by Miss M. A. Butcher, working under a grant from the Endowment Fund of the Birmingham United Hospitals, and we would like to thank Messrs. Glaxo Ltd. for instruction and advice in this method. Mr. J. P. Henry, M.Sc., for invaluable help with the mathematics, and Miss M. N. Ellis for secretarial assistance. Miss B. J. Burden, Miss P. J. Dickens, and Mr. A. L. Tapparo kindly acted as subjects for the survey.

REFERENCES

- Behrens, O. K., *et al.* (1948). *J. biol. Chem.*, **175**, 794.
Brandl, E., Giovannini, M., and Margreiter, H. (1953). *Wien. med. Wschr.*, **103**, 602.
British Medical Journal, 1956, **1**, 282.
Cathie, I. A. B., and MacFarlane, J. C. W. (1953). *British Medical Journal*, **1**, 805.
Giovannini, M. (1954). *Wien. med. Wschr.*, **104**, 910.
Henry, L., and Meynell, M. J. (1956). *Postgrad. Med. J.*, **32**, 297.
Jones, W. F., and Finland, O. M. (1955). *New Engl. J. Med.*, **253**, 754.
Lancet, 1956, **1**, 272.
Martin, W. J., Nichols, D. R., and Heilman, F. R. (1955). *Proc. Mayo Clin.*, **30**, 467, 521.
Sjoberg, S. G., Brante, G., and Regner, K. G. (1955). *Svenska LäkT.*, **52**, 83.
Spitz, K. H. (1955). *Wien. klin. Wschr.*, **67**, 212.
Wright, W. W., Kirshbaum, A., Arret, B., Putnam, E., and Welch, H. (1955). *Antibiot. Med.*, **1**, 490.

RAPID INTRAVENOUS TRANSFUSIONS IN CHILDREN

BY

LESLIE G. ANDREWS, M.B., D.C.H.

Paediatric Registrar, Institute of Child Health, Hammersmith Hospital and Postgraduate Medical School; Formerly Resident Medical Officer, Paediatric Department, St. George's Hospital, London

AND

DAVID J. COLEMAN, M.B., F.F.A.R.C.S., D.A.

First Assistant, Department of Anaesthesia, St. George's Hospital, London

Bayliss and Starling (1894) showed that rapid injections of crystalloid solutions and blood caused a rise in venous pressure in dogs. Previous cord transections at the level of T1 had increased the capacity of their vascular system by one-quarter. In 1918 Starling pointed out that transfusions in anaemic patients caused the heart to behave as an overloaded heart-lung preparation, giving further rise to an already elevated venous pressure. This resulted in a fall of cardiac output and pulmonary oedema. Cabot (1926), Ellis and Faulkner (1939), and Sharpey-Schafer (1944) found the cardiac silhouette enlarged on radiological examination, electrocardiographic changes, and increased cardiac weight at necropsy in

anaemic patients. Sharpey-Schafer and Wallace (1942b) found increased cardiac diastolic size and electrocardiographic changes after transfusions in normal patients. In fatal cases necropsy has shown pulmonary oedema and cardiac dilatation (Plummer, 1936; Fishberg, 1937; Drummond, 1943). According to Riddell (1939) the commonest cause of fatality following blood transfusion is circulatory failure secondary to overloading.

This paper is a report on three anaemic children to whom 16 very rapid transfusions—35–50 ml. a minute—were given under general anaesthesia. There were no ill effects.

Case Reports

Case 1.—A boy aged 6, weighing 2 st. 1 lb. (13.2 kg.) and 3 ft. 8 in. (112 cm.) in height, with congenital hypoplastic anaemia, had a systolic murmur most clearly audible in the pulmonary area, and a liver enlarged to three fingerbreadths below the right costal margin. By May, 1955, he had received a total of 51 transfusions. Initially these consisted of 50 ml. of whole blood, but later he was being transfused with the packed cells from 1 pint (570 ml.) of blood. These earlier infusions were administered under basal narcosis—rectal thiopentone, 1 g. per 50 lb. (22.5 kg.) body weight—given in 20–30 minutes. Splenectomy in March, 1955, brought no improvement. Since June, 1955, he has received nine rapid transfusions under general anaesthesia, each consisting of the fresh packed cells from 2 pints (1,140 ml.) of blood. Blood-volume estimations were performed on three occasions.

Case 2.—The patient was a boy aged 7 weighing 3 st. 11 lb. (25 kg.) and 3 ft. 6 in. (107 cm.) in height, with congenital hypoplastic anaemia, probably of the Fanconi (1927) type—that is, with small head and pigmentation, though this latter may have been due to early haemochromatosis. The heart and respiratory systems appeared normal, but the liver was enlarged to two fingerbreadths below the right costal margin. By June, 1955, he had received a total of 93 intravenous blood infusions consisting of 50 ml. of whole blood, and later the packed cells from 1 pint (570 ml.) of blood. The operation was conducted under basal narcosis—rectal thiopentone, 1 g. per 50 lb. (22.5 kg.) body weight—and completed in 20–30 minutes. Splenectomy in May, 1953, produced no improvement. Since June, 1954, six very rapid transfusions have been given under general anaesthesia, each consisting of the fresh packed cells from 2 pints (1,140 ml.) of blood. On three occasions blood-volume estimations were performed and venous pressure changes were recorded manometrically once.

Case 3.—A girl aged 4, weighing 2 st. (12.7 kg.) and 3 ft. 3 in. (99 cm.) in height, had a neuroblastoma of the left adrenal gland. The cardiac and respiratory systems were normal. She had received two previous slow transfusions each consisting of 1 pint (570 ml.) of whole blood. We transfused her rapidly once under general anaesthesia with 1 pint (570 ml.) of whole blood.

Method

Each child was given a fat-free diet for 18 hours before transfusion. Pentobarbitone sodium, 0.6 gr. per stone (6 mg. per kg.), was given one hour before operation, and atropine, 1/100 gr. (0.65 mg.) hypodermically, half an hour pre-operatively. A quiet induction of anaesthesia was achieved with nitrous oxide, oxygen (30%), and trichlorethylene, and maintenance was with nitrous oxide, oxygen (30%), and ether. A Dinsdale (1954) respirator was used in order to assure minimal resistance to respiration. A high flow of gases was maintained in order to prevent accumulation of carbon dioxide.

The apparatus for transfusion was of a modified scalp vein type with Luer-Lock fittings (see Fig.) (Black *et al.*, 1951; Mollison, 1951). The packed cells were usually

capillary and venous systems. Their findings were based on observations on the pulse, skin circulation, and total peripheral resistance following acute haemorrhage. Altschule and Gilligan (1938) noted skin flushing and a bounding pulse after transfusions in adults, and Russell (1947) observed skin flushing and local heat without venous engorgement after giving blood to children at the rate of 5 ml. a minute.

Sharpey-Schafer and Wallace (1942b), however, had produced evidence to show that the peripheral and pulmonary capillaries and veins dilate to accommodate the increased blood volume. The reason for administering venous transfusion slowly to anaemic patients is to enable the slow adjustment of venous filling pressure to the extra volume given (Sharpey-Schafer, 1945). We believe that ether anaesthesia may lower venous vasomotor tone in children so that the venous side can not only accommodate the blood much more quickly but is probably adjusted to receive it before the transfusion is given. Furthermore Fieldman *et al.* (1955), in a study of 11 adult cases, found a decrease in blood volume on induction of anaesthesia—calculated from the Stewart (1921) formula. A further significant decrease in blood volume occurred on deepening the anaesthesia. There was no significant increase in blood volume on emergence from deep anaesthesia.

The decrease in blood volume in chronic anaemia is an active process by which available haemoglobin is concentrated. This increases the availability of oxygen (Sharpey-Schafer, 1944), allowing the minimum necessary minute-volume cardiac output. Our results showed that in the anaemic phase in children the blood volume was approximately average or actually increased compared with the heights and weights of normal control children (Russell, 1949) (see Table II). Russell's figures and those of Bakwin and Rivkin (1924), however, show a wide range of normality in healthy children.

TABLE II

Case No.	Weight	Height	Average Blood Vol. for Patient's Weight	Average Blood Vol. for Patient's Height	Lowest Blood Vol. Pre-transfusion
1	13.2 kg.	112 cm.	1,100 ml.	1,600 ml.	1,316 ml.
2	25 "	107 "	2,100 "	1,400 "	1,959 "

Russell (1949) thought that the blood volume related to height was more valuable than when related to weight, as when the volume is increased owing to congestive failure the weight would rise automatically. Russell (1947), using a concentrated corpuscle-haemoglobin method for determining blood volumes (Hill, 1941; McMichael *et al.*, 1943), found that blood transfusion to an anaemic child with an initial low blood volume for its height and weight resulted in an increased total circulating volume. In another anaemic child with a high initial blood volume, transfusion resulted in a shift of fluid to the tissues. In our Cases 1 and 2, where the initial blood volume was average or high, transfusion resulted in an increase in the total circulating volume. The percentage increase in volume (Table I) was higher than expected from the quantity of blood given (on all occasions except one in Case 2). A low blood volume does not occur in chronically anaemic children as it does in adults. If the haemoglobin is allowed to fall below 25%, the blood volume may then follow the adult pattern. It can be argued that if the blood volume is reduced before transfusion then an infusion will give a relatively big increase in circulating fluid; if, however, the blood volume is normal or high to begin with, the proportional increase in volume will be less and so the risk of overloading diminished.

Plasma Changes

Sharpey-Schafer and Wallace (1942a) have shown that when blood volume is at a normal level transfused serum leaves the circulation in from one to two hours. Where the initial blood volume is reduced the transfused serum is retained in the circulation. Marriott and Kekwick (1936)

found that where whole blood is transfused in patients with chronic anaemia the added plasma may disappear even during the transfusion, and particularly if it is given slowly. Following our transfusions of packed cells the plasma volume was always increased ten minutes after the termination of the infusion. Russell (1947) suggests this increase in volume may be partly due to differences in the plasma protein levels of the blood of the donor and recipient. Metcalf (1944) found that, in dogs, if the blood of the donor has a higher protein content than that of the recipient, fluid is likely to be withdrawn from the tissues to equalize the osmotic pressure. Conversely, transfused blood of lower osmotic pressure would tend to cause a shift of fluid to the tissues.

Sharpey-Schafer and Wallace (1942a) showed that the rate of disappearance of injected serum depended upon the initial blood volume and not on its protein content. Boycott and Oakley (1934), using cats, and Hayward and Jordan (1942), using human subjects, showed that movement of plasma proteins probably occurs simultaneously with the fluid shift. There is no plasma protein change during haemodilution following acute haemorrhage (Wallace and Sharpey-Schafer, 1941). As we used packed cells the plasma protein content is probably not the main cause of the extra fluid shift from tissues to circulation. Furthermore, there is no substantial loss of injected red blood cells for the first two days after blood transfusions, any volume change being one of plasma (Boycott and Oakley, 1934). The extra plasma could not have come from the spleen in Cases 1 and 2 as they had been splenectomized. Splanchnic or hepatic blood (both cases had large livers) is a possible source. It is unlikely to come from the venous side because of the reduced vasomotor venous tone resulting from the ether anaesthesia.

Quantity and Rate of Transfusion

The signs of an overloaded circulation are an elevated jugular venous pressure (Lewis, 1937) and basal rales (Drummond, 1943). DeBaakey (1938), in over 5,000 transfusions, never once observed the so-called phenomenon of speed shock (Hyman and Hirshfeld, 1931), and not infrequently 650 ml. was transfused in three minutes. In normal hearts Coughy (1935) found that 1,500 ml. of saline at 50 ml. a minute gives no venous pressure rise, but Altschule and Gilligan (1938) found that when more than 500–1,500 ml. of fluid is injected at greater than 26 ml. a minute the venous pressure, cardiac output, and blood volume increased. The faster the rate and the larger the quantity of fluid given, the higher was the venous pressure. Beattie and Collard (1942) found no changes of venous pressure by direct measurement in cases of diabetic coma and post-operative shock receiving similar large transfusions. Sharpey-Schafer and Wallace (1942b) found that 2,000 ml. of saline, serum, or blood can be given to normal hearts at 160 ml. a minute, but again with some rise in venous pressure. Previous reduction of blood volume by venesection prevented this rise. Marriott and Kekwick (1940) advised 1 ml. per 1 lb. (450 g.) body weight per hour to severely anaemic patients (haemoglobin less than 25%), uncomplicated by acute haemorrhage, and did not think it was safe to increase the rate if packed cells instead of whole blood were used. Sharpey-Schafer (1945) showed that 500 ml. at moderate rates (18 ml. a minute) may overload the anaemic heart.

We have found in three cases that 500 ml. could be safely given under general anaesthesia to children in approximately 10–15 minutes—that is, 35–50 ml. a minute. On one occasion this quantity was given direct into the internal jugular vein in ten minutes. This involves infusing two to four times faster than that thought likely to overload the chronically anaemic adult heart. We would not entertain such a rapid transfusion in proved pathologically abnormal hearts—for example, a case of pernicious anaemia—where rapid transfusions under any circumstances would be dangerous. Anginal symptoms may occur in severe anaemia even in normal hearts (Pickering and Wayne, 1934). Hunter (1946) found that, after correction of chronic anaemia,

cardiac pain and enlargement and electrocardiographic changes may persist and be almost identical to the signs of organic heart disease. Thus in chronic anaemia, even when the heart appears normal, ischaemic changes may already have occurred. This, however, seems unlikely to be the case in children.

Summary and Conclusions

A method is described of rapid intravenous transfusions to children. The procedure is regarded as safe in children with clinically normal hearts. It may be particularly indicated where regular transfusions are required during the child's life.

In children with chronic anaemia the blood volume does not fall as in adults. The relative volume increase after transfusion is thus small.

More blood can be given and at a faster rate owing to a reduced blood volume resulting directly from ether anaesthesia, and probably a release of venous vasomotor tone.

The young chronically anaemic heart can withstand fast transfusions better than adult hearts. In selected children transfusions can be given with safety two to four times faster than the rate causing a falling cardiac output in chronically anaemic adults.

The blood volume soon after transfusions is greater than can be accounted for by the volume of blood given; the extra volume may come from the splanchnic or hepatic pools.

We wish to thank Dr. C. Pinckney and Dr. G. Edwards for their encouragement and advice, and Mr. J. G. Davis, Miss S. Fry, and Mr. L. G. Jones for technical assistance. The blood-volume estimations were done by Dr. C. B. Cameron.

REFERENCES

- Altschule, M. D., and Gilligan, D. R. (1938). *J. clin. Invest.*, **17**, 401.
 Bakwin, H., and Rivkin, H. (1924). *Amer. J. Dis. Child.*, **27**, 340.
 Barcroft, H., Edholm, O. G., McMichael, J., and Sharpey-Schafer, E. P. (1944). *Lancet*, **1**, 489.
 Bayliss, W. M., and Starling, E. H. (1894). *J. Physiol. (Lond.)*, **16**, 159.
 Beattie, J., and Collard, H. B. (1942). *British Medical Journal*, **2**, 301.
 Black, M. L., Carré, I. J., and Wolff, O. H. (1951). *Lancet*, **2**, 19.
 Boycott, A. E., and Oakley, C. L. (1934). *J. Path. Bact.*, **38**, 91.
 Cabot, R. C. (1926). *Facts of the Heart*. Philadelphia.
 Caughey, J. L. (1935). *Proc. Soc. exp. Biol. (N.Y.)*, **32**, 973.
 Crooke, A. C., and Morris, C. J. O. (1942). *J. Physiol. (Lond.)*, **101**, 217.
 DeBakey, M. (1938). *Surgery*, **3**, 914.
 Dinsdale, T. (1954). *Anaesthesia*, **9**, 206.
 Drummond, R. (1943). *British Medical Journal*, **2**, 319.
 Ellis, L. B., and Faulkner, J. M. (1939). *New Engl. J. Med.*, **220**, 943.
 Fanconi, G. (1927). *Jb. Kinderheilk.*, **117**, 257.
 Fieldman, E. J., Ridley, R. W., and Wood, E. H. (1955). *Anesthesiology*, **16**, 478.
 Fishberg, A. M. (1937). *Heart Failure*. London.
 Fletcher, G., and Pender, J. W. (1954). *Fed. Proc.*, **13**, 354.
 Gibson, J. G., jun., and Evans, W. A., jun. (1937). *J. clin. Invest.*, **16**, 851.
 — and Gregersen, M. I. (1935). *Amer. J. Physiol.*, **113** (Proc.), 50.
 Harington, C. R., Pochin, E. E., and Squire, J. R. (1940). *Clin. Sci.*, **4**, 311.
 Hayward, G. W., and Jordan, A. (1942). *British Medical Journal*, **1**, 462.
 Hill, D. K. (1941). *Lancet*, **1**, 177.
 Hunter, A. (1946). *Quart. J. Med.*, **15**, 107.
 Hyman, H. T., and Hirschfeld, S. (1931). *J. Amer. med. Ass.*, **96**, 1221.
 Lewis, T. (1937). *Diseases of the Heart*. London.
 McMichael, J., Sharpey-Schafer, E. P., Mollison, P. L., and Vaughan, J. M. (1943). *Lancet*, **1**, 637.
 Marriott, H. L., and Kekwick, A. (1936). *Proc. roy. Soc. Med.*, **29**, 337.
 — (1940). *British Medical Journal*, **1**, 1043.
 Metcalf, W. (1944). *J. clin. Invest.*, **23**, 403.
 Mollison, P. L. (1951). *Blood Transfusion in Clinical Medicine*. Oxford.
 Pickering, G. W., and Wayne, E. J. (1934). *Clin. Sci.*, **1**, 305.
 Plummer, N. S. (1936). *British Medical Journal*, **2**, 1186.
 Riddell, V. H. (1939). *Blood Transfusion*. London.
 Russell, S. J. M. (1947). *Arch. Dis. Childh.*, **22**, 50.
 — (1949). *Ibid.*, **24**, 89.
 Sharpey-Schafer, E. P. (1944). *Clin. Sci.*, **5**, 125.
 — (1945). *Lancet*, **2**, 296.
 — and Wallace, J. (1942a). *Lancet*, **1**, 699.
 — (1942b). *British Medical Journal*, **2**, 304.
 Starling, E. H. (1918). *Linacre Lecture on the Law of the Heart*. London.
 Stewart, G. N. (1921). *Amer. J. Physiol.*, **58**, 20.
 Wallace, J., and Sharpey-Schafer, E. P. (1941). *Lancet*, **2**, 393.
 Wiener, A. S. (1943). *Blood Groups and Transfusion*. Springfield.
 Wood, P. (1950). *Disease of the Heart and Circulation*. London.

GREAT AURICULAR NEUROTOMY FOR TIC DOULOUREUX

A CONTROLLED CLINICAL TRIAL

BY

JOHN PENMAN, M.B., M.R.C.P.

Neurologist, the Royal Marsden Hospital, London

AND

L. S. WALSH, M.B., F.R.C.S.

Research Assistant to the Department of Neurosurgery,
St. George's Hospital, London

Tic douloureux can at present be cured by any of several methods, all of which depend on interruption of those pain-conducting nerve fibres which pass from the ganglion of the trigeminus to the nucleus of its descending tract. All therefore cause some lifelong trigeminal sensory loss, which in most cases entails lifelong facial dysaesthesiae, and each has at least one of these further drawbacks: a more than negligible death rate, an insufficiently high success rate, and a risk of neuromyolytic keratitis or of lesions of other cranial nerves besides the fifth. For many years there has been a search for a cure—or even a means of prolonged relief—without such drawbacks, the two latest operations, which are both still unproved, being trigeminal “decompression” and compression.

Wyburn-Mason (1953) reported that he had treated about 56 patients suffering from tic douloureux by interruption of the great auricular nerve. Each of them first received an alcohol block of that nerve, and about half were completely relieved, “provided the tongue was not involved. . . . The treatment does not relieve the pain in the tongue.” Regarding the periods of complete relief thus obtained, he wrote: “In cases treated by alcohol block alone the pain may return after 6 to 18 months.” When the pain had returned, or if it had not been initially relieved, he treated it in some cases by a further alcohol block and in others by surgical section of the nerve.

Twenty-five of his patients received this surgical treatment, of whom two, at the time when he wrote, had had some return of pain, one two and a half years and the other three and a half years after nerve section. His follow-up was for as long as five years, which presumably means that five years was the maximum, but he did not state the minimum period.

Here, one might think, is the long-sought remedy without serious drawbacks, except for its failure to relieve pain in the tongue. Of the two ways of interrupting the great auricular nerve, Wyburn-Mason evidently prefers surgical section, and we agree with him, for with only a little more trouble than alcohol injection it produces a more certain interruption and a permanent one. Anything which it fails to do, injection likewise will fail to do. We have therefore subjected great auricular neurotomy to a controlled clinical trial on the lines recommended by Hill (1951).

Present Trial

Definitions.—Throughout the remainder of this paper neurotomy means great auricular neurotomy, and injection means alcohol injection of the trigeminal sensory root. Entry-injection interval means the interval between the date of a given patient's entry into the trial and the date of his injection.

Purpose of Trial.—The trial was primarily designed to answer the following question. Suppose that a patient with tic douloureux (1) after hearing the pros and cons of injec-