monitoring at short notice and to remove others from the list when their time of trial is over.

Anaesthesia and Radiology.—Two of the most active fields of research into new drugs are anaesthesia and radiology. About 10,000,000 anaesthetics a year are administered in this country, and in the average 700-bed teaching hospital there will be 10,000 anaesthetics a year. There are two special features of anaesthetics and of diagnostic agents used in radiology which make them of interest to our committee. They are not usually supplied on individual prescription from the pharmacy but from stocks kept in the operating theatres and x-ray departments and would therefore bypass our new monitoring mechanism. Secondly, while anaesthetists and radiologists are on the watch for immediate or early reactions they will not normally have the opportunity to observe delayed reactions. If, therefore, there was a delayed reaction which occurred two to three months later, like homologous serum hepatitis after transfusion or aplastic anaemia after gold or chloramphenicol, it might well be missed. Records of anaesthetics and diagnostic reagents used in radiology are, of course, already kept, but anaesthetists and radiologists are now carrying out pilot studies to see whether data such as the identification of the patient, the drug used, the dose and batch number where applicable, and the occurrence of reactions can be collected in a standardized form and made easy to retrieve. Fortunately the hospitals to which new drugs in these categories have been supplied can usually be quickly pinpointed.

Summary

Adverse reactions to drugs can be divided into intolerance, allergy, and idiosyncrasy. With modern methods of testing before marketing, severe and unexpected adverse reactions to new drugs should be uncommon and deaths from intolerance or anaphylaxis should be avoidable by ordinary therapeutic caution.

Idiosyncratic reactions may not be discovered till a drug is marketed on a large scale. For this reason a period of surveillance is necessary, during which new drugs are kept under special scrutiny and adverse reactions are promptly reported.

Non-fatal or mild reactions to drugs are relatively frequent. It is important that they should be reported so that the relative frequency of their occurrence with different drugs of similar action can be revealed and the more toxic ones can be discarded.

The methods at present being used by the Committee on Safety of Drugs are described. The determination of the ratio between the frequency of reactions (the numerator) and the number of patients treated with a drug (the denominator) is at present difficult, but with the steady improvement in the recording and processing of data in the National Health Service it should become progressively easier.

The opinions expressed in this paper are personal but the work it refers to has almost entirely been done by others. I must therefore declare my indebtedness to my colleagues on the Committee on Safety of Drugs, its secretariat, and the Subcommittee on Adverse Reactions, with whom I have worked so happily and from all of whom I have learned so much.

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Heller-valve Method of Intravenous Fluid Administration in Neonatal Surgery

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Accurate administration of intravenous fluid in the newborn infant can present one of the major problems of paediatric surgery. It is often extremely difficult to adapt the usual "gravity-drip" system to the relatively minute fluid requirements of the infant. A drip rate of as low as 2 ml. per hour is almost impossible to regulate, and predisposes to clotting within the vein, cannula, or both. The flow rate is also sensitive to change in the infant's posture and to the effects of temperature and viscosity variations. By incorporating a form of burette, or graduated chamber, in the drip set, Rickham (1959) facilitated greater accuracy, but constant supervision and adjustment was required, and the likelihood of early vein/cannula thrombosis was unaffected.

The problems of efficient intravenous infusion are equally apparent during operation. It is not uncommon to find the anaesthetist wriggling under the operation drapes, trying to revive a stubborn "drip" so that he can then resuscitate the infant. The need to have a reliable route available for the administration of blood, sometimes rapidly, during major surgery in infants has been emphasized in a leading article in the *British Medical Journal* (1964). This need was dramatically illustrated in the account of the operations for the separation of craniopagus twins (Ballantine and Jackson, 1964). During one such operation no less than 10 litres of blood was transfused. It is probably fair to say that the administration of blood and other fluids has often proved as troublesome as the operation itself.

It was therefore a welcome relief to the surgical and nursing staff of this hospital when our colleagues in the anaesthetic

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department devised a technique which overcame most, if not all, of the above difficulties (Thomson, 1961). In 1958 Heller had published his description of a small, cheap, easily sterilized intravenous adapter or valve which could be fitted to any Luer-size needle. The valve was similar in principle to that of a cycle tyre, and prevented reflux of blood into the needle, which could be left in a suitable vein during operation, permitting repeated injections to be made through it. Heller's aim was to avoid the need for multiple venepunctures or the expensive use of special needles, and the valve was intended specifically for use by anaesthetists only during operation. Thomson, however, saw further possibilities for the valve. He made the most useful observation that at the end of an operation a Heller valve could be left attached to the intravenous cannula, which was now available for post-operative fluid administration.

Since its inception in the surgical division of this hospital in 1960 the Heller valve has proved invaluable in the management of the newborn, and, indeed, older infant, and its use is now routine (Auld and Munro, 1962). It is the purpose of this communication to describe our experience with the valve, in the belief that other centres may also find it useful.

Apparatus

The assembled Heller valve (Fig. 1) measures 3.4 cm. long by 0.8 cm. in diameter. It comprises a proximal and a distal metallic tube which screw together, forming a central hollow chamber. Within this chamber a thin rubber sleeve over the "core" of the proximal segment covers the valve aperture. During injection the sleeve lifts and allows fluid to enter the chamber and pass through the distal segment of the valve. When the injection is completed the sleeve effectively occludes the valve aperture and prevents reflux. The valve is easily cleaned, sterilized by boiling (*not* autoclaving), and stored in any suitable antiseptic solution. It can be used repeatedly, but after long service it loses full efficiency owing to wear in the rubber sleeve or to the washer sealing the central chamber. Reflux of venous blood into the cannula is then seen and the valve should be replaced and discarded.

FIG. 1.—The Heller valve. When unscrewed into its two sections (above) the rubber sleeve covering the aperture in the valve core can be clearly seen. The black ring (above and below) is the rubber washer sealing the central valve-chamber.

Methods of Use

A polythene intravenous catheter of suitable calibre is inserted with aseptic precautions into the saphenous vein at the ankle or into a vein in the antecubital fossa. The usual "cut-down" technique is employed and the catheter inserted for about 3 in. (7.5 cm.) within the vein. After closing the wound with fine silk an occlusive dry dressing is applied and the valve-infusion system instituted by one of the following methods.

(a) *Valve Alone.*—The original and simplest procedure was to attach a Heller valve to the intravenous cannula and inject the required amount of fluid at hourly intervals (Fig. 2). The injection takes only a few seconds to perform, and the syringe is then disconnected. To prevent bacterial contamination of the exposed valve socket a second sterile valve can be inserted to act as a "plug" until the next injection is made. Care is, of course, taken to avoid touching either the valve socket or the nozzle of the syringe.

FIG. 2.—The simplest method of using the Heller valve, in which it is directly attached to the intravenous cannula.

(b) *Valve and Extension Tube.*—In order to minimize the handling and disturbance of the cannula itself at each injection, and to enable injections to be performed outside the incubator, a plastic extension tube can be inserted between the valve and the cannula (Fig. 3). The tube is 30 in. (76 cm.) long, has a capacity of less than 2 ml., and is supplied pre-sterilized. The emptied syringe can be left attached to the valve to act as a sterile plug until the next injection. During operation this apparatus is used by the anaesthetists, who can thus give all intravenous drugs and fluids from the head of the table without disturbing sterile drapes (Auld and Munro, 1962).

FIG. 3.—The addition of an extension tube permits fluid administration from outside an infant's incubator.

(c) *"Closed Circuit."*—A further simple modification has been devised by our nursing staff, and obviates the need to disconnect and load syringes at each injection. It also overcomes the possible dangers of bacterial contamination of either

FIG. 4.—The "closed circuit" method, utilizing drip-set, three-way tap, valve, and extension tube.

the valve or the "donor" bottle. An ordinary drip set and a three-way tap and syringe are attached to the valve and extension set already in use (Fig. 4). The syringe is filled and discharged via the tap at hourly intervals, or as required, and separate injections of any other kind can, of course, be made through the three-way tap after detaching the "resident" syringe.

Results

The Heller valve has now been in use for over five years in the surgical division of this hospital. Initially it was employed solely in the newborn infant, but recognition of its advantages has led to its use in older children too. The cases treated have included all newborn and young infants undergoing emergency or elective surgery in whom replacement of blood, plasma, or electrolytes was indicated. The amount and rate of the infusion was determined by the infant's particular needs, as little as 1 ml. per hour being given post-operatively in some patients. In at least seven cases the infusion was maintained for over a week without blockage occurring (see Table).

Incidence of Complications in 500 Infusions in which the Heller Valve was Employed

No. of Infusions:	Duration of Infusion (Days)				Total
	0-1	1-2	2-7	Over 7	
	48	292	152	8	500
"Mild" thrombophlebitis ..	7 (15%)	36 (12%)	65 (43%)	5 (62%)	113 (23%)
Thrombophlebitis and blockage ..	3 (6%)	28 (10%)	12 (8%)	1 (12%)	44 (9%)
Blockage alone ..	4 (8%)	5 (2%)	2 (1%)	1 (12%)	12 (2%)
Deep venous thrombosis ..	0	0	1 (0.5%)	0	1 (0.2%)
? Septicaemia ..	0	0	1 (0.5%)	0	1 (0.2%)
Total ..	14 (29%)	69 (24%)	81 (54%)	7 (87%)	171 (34%)

Since the valve-infusion technique has been adopted it is estimated that over 1,200 intravenous infusions have been administered with one or other of the above methods. On the basis of this experience the following observations appear pertinent.

1. *Simplicity*.—The apparatus has given the nursing staff little trouble to operate, and has greatly reduced the time spent supervising and coaxing reluctant drips. It has met with wholehearted approval by all concerned with its day-to-day care.

2. *Accuracy*.—The use of graduated syringes obviously permits a high degree of accuracy in the rate of fluid administration. As little as 1 ml./hour has been given.

3. *Reliability*.—Provided the cannula is inserted with the usual precautions and injections are made at intervals of one hour or less, the circuit will remain patent for many days (see Table). Each injection flushes the vein in use, as opposed to the slow "ooze" of the gravity-drip system, and helps to delay thrombosis. Venous spasm is of no significance.

4. *Rate of Injection*.—Amounts of up to 5 ml. fluid per kg. body weight have been given at a single injection without ill effect, though with these larger amounts it seems prudent to extend the duration of the injection to two or three minutes. Much larger volumes of blood can be injected in a very short time if loss of blood during operation is excessive, and the need for elaborate pumping apparatus—often difficult to control—has been completely dispensed with. The precautions to be observed during such blood replacement, with regard to the effects of citrate and potassium content, and temperature of the blood given, have been discussed elsewhere (Thomas, 1964; Graham, 1964). Again the advantage of accurate measurement of the transfusion has proved inestimable.

5. *Versatility*.—The Heller valve has several other uses. It can be attached to an intravenous cannula in older children,

as a temporary measure, during transfer of the patient to theatre, another ward, radiotherapy or radiodiagnostic department, or even to another hospital. In infants and other patients where repeated venepuncture is difficult, and where daily administration of intravenous drugs, such as cytotoxic agents, is desired, an intravenous cannula can be maintained *in situ* for days.

Complications

The possible complications of any intravenous infusion are concerned broadly with infection and/or blockage. The former may be due to contamination at the time of the actual insertion of the cannula, or to subsequent access of organisms into the wound and hence into the vein alongside the cannula. It may also arise from some contamination within the infusion apparatus itself, resulting in direct intravenous bacterial injection, thrombophlebitis, and even septicaemia with metastatic abscess formation. Theoretically at least, the Heller-valve technique would seem to be more likely to run the risk of intraluminal infection, owing to repeated injections through the valve, and this was the prime reason for adopting the "closed circuit" method, although there had been no obvious increase in infection with the earlier systems. Blockage without infection has been a rare occurrence when using the valve, presumably for the reasons stated earlier.

In order to assess the incidence of complications the case records of patients who had received valve-infusions in the three-year period 1962 to 1964 (inclusive) were reviewed and the results in 500 infusions analysed. These had been given to a total of 319 infants, some of whom had several separate infusions. The cases were selected only because their records were sufficiently detailed to give accurate information regarding the infusions; most had been seen by me during their stay in hospital. Their ages ranged from a few hours to 3 years, the majority being in the neonatal period.

The results are shown in the Table. Infection of the actual "cut-down" wound itself has not been included; mild degrees of such infection were undoubtedly common but usually insignificant, and would be produced, not by the mode of infusion, but by local factors common to the insertion of any intravenous cannula.

(a) *"Mild" Thrombophlebitis*.—The term "mild" has been used where there was local redness over the cannulated vein but no blockage to the infusion fluid. Often the redness extended proximally from the "cut-down" wound, and represented external contamination rather than infection *via* the Heller valve, but all such cases have been included. No specific treatment was required. Nearly all the patients were receiving prophylactic antibiotics post-operatively, and some cases included in this and the following group probably had an aseptic chemically induced phlebothrombosis rather than thrombophlebitis. Though the incidence (23%) is substantial, the condition had little, if any, adverse effects on the patient, and is probably no more common than in conventional gravity-drip methods. As one would expect, this complication was more common in the longer-term infusions.

(b) *Thrombophlebitis with Blockage*.—In these cases the external appearances differed little from those in (a), and the infant was no more upset, but as the infusion was blocked it has been implied that the pathological changes within the vein have been more serious. More frequently the redness originated at or near the tip of the cannula, indicating that the source of infection and/or chemical irritation has been the intravenous fluid itself. In this category, therefore, infection due to contamination of the valve may well be implicated, though other factors, as above, cannot be excluded. The incidence of this complication (9%) is not high *per se*, nor has it seemed higher in comparison with previous experience with conventional methods of the newborn infant. As in (a), no specific treat-

ment was required and no case progressed to local abscess formation.

(c) *Blockage Alone*.—This occurred without evidence of inflammation in only 12 cases (2%). Usually there was evidence that the tip of the catheter had pierced the vein wall, causing extravasation. In order to facilitate introduction of the polythene cannula into the tiny veins of the infant, the tip of the cannula is often trimmed obliquely by the surgeon, and is probably the main reason for this accident. A "sharp-pointed" cannula should therefore be rounded off before introduction.

(d) *Deep Venous Thrombosis*.—Generalized oedema of the cannulated limb occurred in one case only on the fourth day, and the infusion was stopped. There was only slight redness of the infused vein, and no absolute conclusions can be drawn. The infant was 5 days old, was not given anticoagulants, and recovered uneventfully.

(e) ? *Septicaemia*.—One four-month-old infant developed septicaemia during the forty-eight hours following a difficult reduction of an ileocolic intussusception. Intravenous fluids were given during this time and were discontinued after 36 hours. There was no obvious thrombophlebitis. Acute osteitis of two long bones ensued, and an abscess developed in the laparotomy wound. A penicillin-resistant strain of *Staphylococcus aureus* was cultured in the pus of all three septic foci; with appropriate treatment the infant made a full recovery. The most probable source of infection was the wound itself, during operation, but the possibility that the organism was introduced via the infusion apparatus, although unlikely, cannot be ruled out.

Conclusion

The Heller valve provides a simple, cheap, reliable, and accurate method of giving intravenous fluids to newborn

infants. Its use reduces the time spent by the medical and nursing staff in supervising intravenous drips in neonates; and it can readily be adapted for other purposes.

Minor complications occur, as with any form of intravenous infusion in infants, but their incidence is not high, and is probably much lower than that associated with earlier techniques. In a series of 500 valve-infusions only two major complications were found which might be attributed to this method.

The valve costs 6s. 9d., which is little more than the cost of a single disposable drip set, and it may be used more than fifty times before leak-back occurs.

Summary

A method of administering intravenous fluids to infants is described and assessed in the light of experience of over 1,200 infusions. The advantages over more conventional methods are discussed and the possibilities of the adaptation of the system for other purposes are indicated.

The Heller valve is manufactured by Medical and Industrial Equipment Ltd., 10/12 New Cavendish Street, London, to whom I am grateful for information and advice. I am also indebted to Mr. J. Devlin for the photographs. I should like to pay tribute to the nursing staff, whose constant care and skill have contributed so much to the well-being of the infants discussed above.

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Coronary Heart Disease in the Aged

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William Heberden (1802) stated that he had seen nearly 100 people with angina pectoris, and all but four were males near or past the fiftieth year of age. We are now uncomfortably aware of the frequency with which the male members of western populations, especially the relatively young, die of coronary heart disease. The death rate from diseases of the heart is said to have changed very little in the years 1850 to 1920, but from 1924 onwards the death rate rapidly increased until about 1952, when it showed signs of levelling off (Campbell, 1963a). This apparent and alarming increase may well be due to the possibility that those who would have died from the infectious diseases now survive longer to die from coronary heart disease, as so lucidly argued by Campbell (1963b). It is doubtful, judging by post-mortem reports, that there has been any absolute increase in the incidence or severity of atheroma over the years 1908–49; the reverse is true if anything (Morris, 1951). There is some evidence that in the elderly the disease is different in its clinical presentation (Dreyfuss, 1959), and it is a comparative rarity to make the diagnosis of a coronary thrombosis in the age group 60–80 years (Howard and Gresham, 1961). Many of the coronary

thromboses in the elderly are "silent" (Rodstein, 1956), and the distribution of the atherosclerotic lesions is different (Wright, 1960).

We were impressed by the rarity with which we saw the clinical entity of acute coronary heart disease in those admitted to an acute geriatric department serving a sizable area of North Central London. In those in whom the diagnosis was made the clinical severity of the episode was marked and the outlook grave. In this paper we present our findings in a three-year retrospective study.

Methods

The case records of all admissions to this 88-bed department over a three-year period were examined, and only those patients who had unequivocal electrocardiographic or post-mortem evidence of a recent—that is, within one week—coronary thrombosis or myocardial infarct were accepted for this study, regardless of the original reason for admission. Electrocardiographs were not taken routinely on admission of all patients, though in practice this was done in fact in a high proportion. We were, of course, aware that cardiovascular disease may present atypically in the elderly, and therefore we readily asked

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