

hypertensive patients, but point out that virtually all these had already been screened by at least one hospital physician before being referred to their care. It is probable that the true prevalence of unilateral renal disease among hypertensive patients is much lower, certainly less than 5%⁴ and possibly as low as 1%. Several clinical criteria have been suggested as likely indicators of secondary hypertension: they include lack of family history, an age less than 40 years, and rapid evolution of severe hypertension. However, A. Breckenridge and colleagues,¹ in a recent detailed study of 229 hypertensive patients younger than 40, pointed out the rarity of unilateral renal disease in this group, who again were selected by having had a previous examination. They found only 12 patients with renal arterial disease (six with stenosis), two with absent kidneys, and one with a renal cyst. Dr. Luke and his colleagues are likewise cautious in their assessment of the value of clinical clues, and this makes the investigation of hypertensive patients all the more necessary. Among the investigations that all hypertensive patients should undergo to assess the severity and origin of the hypertension are a urine test for protein, a blood-urea estimation (supplemented by some simple clearance measurement), and, most important of all, a good intravenous urogram. This should be done in dehydration but include a contrast washout with an increase of urine flow⁵ stimulated by one of several techniques. Tomography of the kidneys may be necessary to show details of both the affected and the presumed normal kidney. In a growing number of hospitals it is possible to perform the valuable investigation of isotope renography.⁶ In a few hospitals renal scanning can be carried out by means of radioactive compounds concentrated in the kidney.⁷ All these procedures can be done on outpatients.

When these techniques suggest that some lesion of one kidney is present, further investigation will be necessary. For these the patient must be admitted to hospital, and because further investigation may require special facilities referral to an experienced centre may be requested. The commonest finding in the preliminary screening is some difference between the kidneys either in size or in rate of excretion. The presence of a unilateral lesion and hypertension does not of course indicate that the hypertension depends on the lesion. An aortogram and selective renal arteriograms are frequently necessary, particularly if renal-artery disease is suspected. Again, the detection of an arterial stenosis does not prove it to be the cause of a raised blood pressure, for many patients have renal-artery stenosis unrelated to their hypertension⁸ or unaccompanied by hypertension.⁹

How can one determine whether the unilateral renal lesion is the cause of the hypertension and that the patient will

benefit from operation? Much has been written on the relation of renal ischaemia (whether in terms of blood flow, diastolic pressure, or pulse pressure) to a rise in the systemic arterial blood pressure.¹⁰ Attempts to assess renal ischaemia have been made in various ways. Direct measurement of pressure drop across the stenosis has been attempted. A functional pattern of ischaemia (an increased reabsorption of filtered salt and water) has been sought by divided renal-function studies¹¹ or the washout pyelogram.⁵ And tests have been devised to detect an increase triggered off by the ischaemia of the hormones, renin, angiotensin, and aldosterone. Careful pyelograms to show the increased concentration of dye on the affected side have made divided renal-function studies less important than formerly. However, a knowledge of the contribution of the affected kidney to total renal function may be essential, as when nephrectomy is unavoidable. Unfortunately, measurement of the concentrations and rates of secretion of the hormones involved are still experimental procedures, but the introduction of an immuno-assay for angiotensin may make their assessment in patients with unilateral renal disease more readily available.

Even with full investigation it is a general experience that operation in some cases, whether on the renal artery or on the kidney itself, will not be successful. An important indication for operation, therefore, is the failure of conventional antihypertensive therapy to control the blood pressure smoothly.¹² Some other patients may be unable or unwilling to co-operate with treatment, and this possibility needs to be carefully considered when treatment is being planned for each patient.

Lung Transplantation

Immunological rejection is likely to remain for some time the most important problem in transplantation surgery. Oddly enough it seems to be unrelated to the complexity of the tissues concerned. For instance, patients have a greater host tolerance for kidney and liver than for skin. But apart from the immunological problem we still have to overcome many other difficulties specific to the individual organs being or likely to be transplanted.

The lung was first completely separated and reimplanted experimentally in 1951.¹ This work established principles that have been exploited on many occasions since. The first report of a technically successful lung homograft in man came in 1963.² The patient survived for 18 days—the longest survival time in man so far. During the last decade a great deal of experimental work has shown that there are two main technical and physiological problems that have to be overcome if lung transplantation is to be successful. Firstly, the lung, unlike the heart with its transplantable built-in mechanism of self-control, depends on a complex voluntary, biochemical, and autonomic nervous mechanism for its proper function. Total denervation results in a type of slow-deep

¹ Breckenridge, A., Preger, L., Dollery, C. T., and Laws, J. W., *Quart. J. Med.*, 1967, **36**, 549.

² Luke, R. G., et al., *Brit. med. J.*, 1968, **2**, 1415.

³ *Brit. med. J.*, 1968, **2**, 327.

⁴ Kennedy, A. C., Luke, R. G., Briggs, J. D. and Stirling, W. B., *Lancet*, 1965, **2**, 963.

⁵ Sutton, D., Brunton, F. J., and Staver, F., *Clin. Radiol.*, 1961, **12**, 80.

⁶ Luke, R. G., Briggs, J. D., Kennedy, A. C., and Stirling W. B., *Quart. J. Med.*, 1966, **35**, 237.

⁷ Reba, R. C., McAfee, J. G., and Wagner, H. N., *Medicine (Baltimore)*, 1963, **42**, 269.

⁸ Lawrence, J. R., Doig, A., Knight, I. C. S., MacLaren, I. F., and Donald, K. W., *Lancet*, 1964, **1**, 62.

⁹ Schwartz, C. J., and White, T. A., *Brit. med. J.*, 1964, **2**, 1415.

¹⁰ Peart, W. S., Chapter 25 in *Renal Disease*, ed. D. A. K. Black, p. 638. 1967. London.

¹¹ Stamey, T. A., Nudelman, I. J., Good, P. H., Schwentker, F. N., and Hendricks, F., *Medicine (Baltimore)*, 1961, **40**, 347.

¹² Dustan, H. P., Meaney, T. F., and Page, I. H., in *Antihypertensive Therapy*, ed. F. Cross, p. 544. 1966. Berlin.

¹ Juvenelle, A. A., Citret, C., Wiles, C. E., jun., and Stewart, J. D., *J. thorac. Surg.*, 1951, **21**, 111.

² Hardy, J. D., Webb, W. R., Dalton, M. L., and Walker, G. R., *J. Amer. med. Ass.*, 1963, **186**, 1065.

³ Hill, P. McN., and Shaw, K. M., *Thorax*, 1968, **23**, 408.

respiratory activity that is perhaps analogous to complete heart block. The only way at present to overcome this problem seems to be by the retention of some part of the host's intact lung to "drive" the graft. Secondly, after transplantation there is a perplexing loss of function at capillary-alveolar level resulting in an early deficiency of ventilation and oxygen uptake in the graft. Though this may improve, function tends to remain well below normal.³ To some extent the loss can be reduced in the experimental animal by increasing the functional load on the transplant by further excision of the remaining normal lung tissue of the recipient. This is a state of affairs of which we understand the principle from the behaviour of heart valve transplants: it seems essential that their function should not be shared. But in addition the loss of lung function may, it seems, at least in part, be due to pulmonary oedema from obstruction of the pulmonary venous drainage.

Technically transplantation of the lung, like that of most other organs, is a relatively easy operation, though it may still be improved, for example, by the addition of bronchial-artery implantation into the aorta, theoretically not a very difficult procedure. Human lung homografts have now been recorded in five patients, including the case described at page 759 of the *B.M.J.* this week by Dr. Henry Matthew and his colleagues at Edinburgh.

Indications for lung transplantation cannot at this stage be laid down, but it would appear that only patients who have a rapidly fatal disease should be considered as recipients, and among these the operation may have to be restricted to patients in whom a certain amount of lung remains intact. Paraquat poisoning would seem to be a good indication, provided sufficient time can be allowed to elapse for the complete elimination of the drug; otherwise the graft may be destroyed.

Finally, study of the clinical and pathological findings in patients after homograft operations suggests that much further research is needed to enable surgeons to distinguish between "inflammations" resulting from bacterial infection, chemical reaction, and rejection processes. Until these can be accurately separated the conclusions that may be drawn from individual cases will be in doubt.

Despite the paucity of long-term survivors among experimental animals and the poor record of human lung homografts so far, this work seems likely to continue. If it does, it should surely be taken along cautiously only in the few centres fully equipped for it, and by teams which have already gained a thorough experience of immunosuppression as at Edinburgh.

A New Anticoagulant

An entirely safe and reliable anticoagulant for the prophylaxis or treatment of thrombo-embolism has yet to be discovered, but recently an entirely new approach to the problem has been made. An enzyme which directly destroys fibrinogen has been extracted from the venom of the Malayan pit viper, *Agkistrodon rhodostoma*. Given intravenously, the enzyme reduces the concentration of fibrinogen in the plasma to very low levels by destroying the protein faster than it can

be synthesized. The oral anticoagulants, such as warfarin or phenindione, depress the hepatic synthesis of clotting factors. Heparin directly inhibits coagulation enzymes, particularly thrombin. In contrast, the anticoagulant effect of the venom enzyme depends on the restriction of fibrinogen, the soluble precursor of fibrin.

Interest in the Malayan pit viper as the source of a therapeutic substance was prompted by H. A. Reid, who observed that bleeding was negligible in patients bitten by the snake, despite a state of defibrination. Their blood was often incoagulable owing to a low concentration of fibrinogen, sometimes for many days.¹ The active principle has now been separated from neurotoxic and vasculotoxic (haemorrhagic) fractions of the venom² and is available for clinical trial as Arvin. Its action is independent of the coagulation and fibrinolytic enzyme systems, and platelets are not affected, in either numbers or function. It is usually assayed in units defined by its ability to clot fibrinogen.

Extensive studies in animals³ and preliminary clinical trials^{4,5} suggest that when defibrination is induced by Arvin spontaneous bleeding from normal tissues is rare and menstrual losses are not increased. Such bleeding as may occur from recent surgical wounds has been easily controlled. This contrasts favourably with the record of the conventional anticoagulants. Animal studies show that the injection of *A. rhodostoma* venom causes the formation of intravascular microclots, which rapidly disappear.⁶ The fibrinolytic enzymes may help in this removal. The weak structure of the clots makes them peculiarly susceptible to lysis, and there is evidence that the macrophages of the reticuloendothelial system play a part. Toxic effects due to obstruction of small blood vessels develop only when the Arvin is given too quickly, so that the removal mechanisms are overwhelmed. The safety margin is wide; in both mice and dogs the lethal dose is 500 to 1,000 times greater than the defibrinating dose.⁷

Occasional hypersensitivity reactions have been reported, and dogs develop some resistance to the enzyme when it is given for long periods. However, no serious reactions have been encountered and no precipitating antibodies detected.⁵

Arvin therefore shows many of the characteristics of the ideal anticoagulant. It causes a predictable, reproducible, and sustained effect, easily controlled by measurement of the plasma fibrinogen or by a simple test of clot quality.⁸ When its administration is stopped its effect is tapered off, which makes "rebound" thrombosis unlikely. The concentration of fibrinogen in the plasma slowly rises to pretreatment levels over several days. If the need arises a rapid return to normal can be achieved by giving a specific antivenom, prepared in horses, and a transfusion of fibrinogen.

Preliminary clinical studies^{4,5} have indicated some of the benefits which can be achieved in the treatment of arterial or venous thrombosis. Controlled clinical trials should not be long delayed.

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² Esnouf, M. P., and Tunnah, G. W., *Brit. J. Haemat.*, 1967, 13, 581.

³ Ashford, A., Ross, J. W., and Southgate, P., *Lancet*, 1968, 1, 486.

⁴ Bell, W. R., Pitney, W. R., and Goodwin, J. F., *Lancet*, 1968, 1, 490.

⁵ Sharp, A. A., Warren, B. A., Paxton, A. M., and Allington, M. J., *Lancet*, 1968, 1, 493.

⁶ Regoeczi, E., Gergely, J., and McFarlane, A. S., *J. clin. Invest.*, 1966, 45, 1202.

⁷ Reid, H. A., in *Animal Toxins*, ed. F. E. Russell and P. R. Saunders, 1967, p. 323. Oxford.

⁸ Reid, H. A., and Chan, K. E., *Lancet*, 1968, 1, 485.