

the kidney came from an unrelated cadaver. In addition, however, different tissues vary in their susceptibility to rejection. Skin is the most difficult tissue graft to maintain with standard immunosuppression and liver the easiest. Heart and lung seem to be liable to aggressive rejection, more so than the kidney. Gaseous exchange through the lungs depends on the integrity of the extremely delicate alveolar lining. It is possible that minor changes of rejection which can be tolerated by heart, liver, and kidney without serious functional upset can cause disastrous changes in alveolar permeability and severely restrict lung function.

Another obvious difference between the lung and other organs that have been grafted is the necessity of exposure of the airway and its ramifications to the atmosphere, and therefore to potentially pathogenic organisms. It is not surprising that many lung grafts have failed owing to infection or a combination of rejection and infection. The normal protection of the airways by ciliary activity and production of mucus may also be impaired as a result of grafting. Interference with the innervation of the lungs is probably more important than with other organ grafts. Dogs are particularly susceptible, and, if both lungs are denervated by transplantation, disturbance of the reflexes that co-ordinate ventilation can result in disorganized breathing, with respiratory failure. To all these difficulties must be added physiological disturbances resulting from the patient's lung disease. Thus, if there is severe pulmonary hypertension, the transplanted lung will have to accommodate nearly all the cardiac output, which may be an unbearable strain on the vasculature of the graft. If the opposite lung is emphysematous, there is a likelihood of increased aeration of the patient's diseased lung at the expense of the graft, which becomes constricted and collapsed by the patient's own distended lung. It is obviously important that the transplanted lung is the right size to be accommodated in the recipient thorax. It has been suggested that both lungs, or the heart and both lungs, should be grafted to obviate these dangers, but the results of these operations have been very disappointing for reasons that are not fully appreciated.

The lung is sensitive to ischaemia, and if left at body temperature for more than an hour without a blood supply severe anoxic damage is likely. The liver and heart are more sensitive, the kidney less.

This catalogue of problems sounds and is daunting, but incapacitating lung disease is extremely common, and many workers are enthusiastically attempting to overcome each of the difficulties.

One encouraging case of F. Derom, in Belgium, is a pointer to a more optimistic direction. The patient, a man of 23, was completely incapacitated with silicosis complicated by infection. He had a  $P_{O_2}$  of 45 and a  $P_{CO_2}$  of 65-70 mm. Hg. He was bedridden and on continuous oxygen. The donor was a 40-year-old patient who died from a cerebrovascular haemorrhage. The right lung was transplanted. It was not subjected to hypothermia, nor was it ventilated or perfused. The total ischaemia time was 50 minutes. The pulmonary veins were anastomosed with an atrial cuff to the recipient's left atrium. After operation the  $P_{O_2}$  was 68 and  $P_{CO_2}$  42 mm. Hg. The patient's condition improved and so did his enjoyment of life. He received undoubted benefit from his transplant, but succumbed to chronic rejection 10 months later. The encouraging results of this operation may have been partly due to the fact that the patient had restrictive lung disease; his own lung therefore could not become overdistended. It also showed that one lung could cope with most of the cardiac output immediately after operation.

## New and Old Friends

The chemical treatment of disease has revolutionized medicine in the life-time of many doctors practising today. Man lives longer on the average and suffers less discomfort than he did about 30 years ago largely owing to the multitude of efficacious remedies introduced since then. At the same time the growth of drug addiction and dependence, the shock of tragedies such as that due to thalidomide, and the emergence of drug-resistant strains of infective organisms are reminders of the price we are paying for therapeutic advance. These are some of the themes reviewed in the latest issue of the *British Medical Bulletin*,<sup>1</sup> edited by Professor D. R. Laurence, of University College Hospital Medical School.

The practising doctor, bombarded as he is with advice on circumstances in which he should or should not prescribe drugs, knows little of what goes on behind the scenes to make one tablet resemble (but how exactly?) another tablet from the same bottle. That a new remedy has been carefully tested before being introduced to clinical practice is well known, but equally familiar is the series of reports during the next year or two of unexpected side effects. What this points to is the extreme difficulty of making inferences from experimental studies that are valid for ordinary clinical practice. Still more unpredictable can be the effect on the fetus of a drug given to the mother, while risks of a different but related kind need to be investigated before a new food additive is introduced. As well as discussing matters of this kind in the *B.M.B.* several expert contributors report on the monitoring of drugs before and after they reach the clinician. The necessity for this is well summed up in a phrase of Sir Derrick Dunlop's—"the shortcomings of new friends are not always immediately obvious."

## Holiday Cholera

As the present epidemic of cholera has moved westwards it has come within range of British tourists. Holidaymakers returning from any part of the shores of the Mediterranean may have been in contact with the disease, since its present extent is not accurately known (see page 653). Tourists staying in modern hotels are unlikely to have been infected, but doctors should be alert to the possibility of cholera in anyone with a gastrointestinal upset within a day or two of returning to Britain from a suspect area.

Most patients infected with *Vibrio cholerae* have no symptoms at all, and many have an upset so mild that they do not realize they have been ill. A slight looseness of the bowels or the passage of two or three semi-formed stools may be the only clinical evidence of infection, and this is easily overlooked or put down to some passing dietary indiscretion. As in so many other infections, the classical clinical picture is the least common manifestation though the most easily recognized. The patient's symptoms come on suddenly with the passage of loose, pasty stools, but soon all faecal matter disappears and the stool becomes entirely fluid. The fluid is clear but with a greyish-white sediment—the "rice-water stool" of cholera. This fluid stool gushes from the patient with little

<sup>1</sup> "Drugs: Development and Use," ed. D. R. Laurence, *British Medical Bulletin*, 1970, 26, No. 3. British Council, 97 & 99 Park Street, London W1Y 4HQ.

gripping pain and quite beyond his control, and with it the patient loses vast quantities of water and electrolytes. Vomiting is common at this stage, effortless and painless, and both vomit and stool are teeming with vibrios. Untreated, this loss of fluid and electrolytes leads within hours or at most a day to dehydration, with loss of skin elasticity, sunken eyes, dry mouth and tongue, and oliguria. It is not long before such dehydration leads to shock, with collapse of blood pressure, rapid shallow respiratory cyanosis, and clammy skin, muscle cramps, and anuria. Unrelieved, the patient rapidly dies, but with skilful treatment the dehydration can be overcome and recovery is speedy.

For a patient with the classical symptoms of cholera laboratory confirmation is scarcely necessary for clinical diagnosis. For the mild or symptomless case there is no other way to diagnose the infection, and as soon as cholera is suspected the co-operation of laboratory staff should be sought. A carefully taken rectal swab can be used for immediate dark-ground microscopy or for fluorescent antibody testing. The former may give a positive result in a few minutes, the latter in an hour or two. From the same swab *V. cholerae* may be grown in nutrient media overnight. The organisms are easy to identify in the laboratory. The difficulty is first to identify the infected patient; the only clue in the mild case lies in the patient's movements. Has he recently come from a cholera area? If he has, then a mild gastrointestinal upset may be due to infection with *V. cholerae*, and laboratory tests are essential to confirm the diagnosis.

## Traps in Tuberculosis

The complications of syphilis and tuberculosis are no longer commonly seen in the neurological wards of our hospitals, their place being taken by the unusual cases of cryptogenic carcinoma, the collagenoses, or metabolic disease. They are thus in danger of being overlooked, for these diseases are still to be seen even if the ways in which they commonly present have altered. In the immigrant population the neurological lesions due to tuberculosis in particular are being seen more frequently again and should come high in the differential diagnosis of obscure meningitides and of spinal syndromes which may be accompanied by a suggestion of meningeal irritation. R. S. Kocen and M. Parsons<sup>1</sup> have recently collected a number of such cases and point out that, whereas typical tuberculous meningitis is unlikely to be misdiagnosed, the same disease may present in a manner confusing to most clinicians yet equally responsive to treatment and equally tragic if unrecognized.

To understand the different types of syndrome one has only to go back to the well-known conception of the Rich focus<sup>2</sup> and realize that a tubercle, not necessarily part of miliary tuberculosis, if situated in the meninges can cause typical meningitis; if in the cerebral cortex, focal fits, and so resemble a cerebral tumour; or if in the cord itself a paraplegia. These early lesions may then be followed by meningitis if the focus later ruptures into the subarachnoid space. K. B.

Taylor, H. V. Smith, and R. L. Vollum<sup>3</sup> showed that the onset of tuberculous meningitis in some cases could be very abrupt, with an unexpectedly high polymorphonuclear count in the cerebrospinal fluid, and that this could settle spontaneously as what was essentially a tuberculin reaction subsided, giving the impression of cure, or perhaps of response to some antibiotic other than streptomycin. Such patients might be sent home only to be readmitted with the inevitable, and sometimes fatal, relapse. They stressed then the necessity for careful examination, repeatedly if necessary, of the cerebrospinal fluid for tubercle bacilli by all available means, and this needs to be re-emphasized now.

Paraplegia is a familiar complication of Pott's disease, but tuberculomata may be present in the spinal cord or the epidural space while routine x-rays appear normal, and sizeable epidural granulomata may be present despite apparently normal films if the lesion is confined to the laminae or pedicles.<sup>4</sup> These are certainly rare. C. Arseni and D. C. Samitca<sup>5</sup> found only nine intraspinal tuberculomata in a 20-year experience of 38,500 neurosurgical patients drawn from a population at high risk, compared to 201 intracranial tuberculomata, while other spinal tumours were 43 times as common. Yet a progressive paraplegia accompanied by or followed by a meningitic reaction must arouse suspicion of this disease immediately, and it may be very responsive to antituberculous treatment. Other cases may simulate spinal metastases or, if in the lumbar region, even simple sciatica. A paraplegia may develop during the course of a recognized tuberculous meningitis. This may be due to an endarteritis and spinal infarction, or to organizing exudate strangulating the vascular supply to the cord, or again to an intramedullary tuberculoma.

R. A. Wiseman and A. Mahmood<sup>6</sup> stress that these lesions are not so uncommon in countries where the disease is more prevalent than in Britain, and they may be seen more often here owing to the increase in movement of populations. One negative test of the cerebrospinal fluid does not exclude tuberculosis in obscure meningitis and paraparesis. A diagnosis of epidural secondaries cannot be accepted as certain without histological confirmation when there is no demonstrable primary malignancy. And it is worth remembering that the cerebrospinal fluid in the early stages of tuberculous infection may show little change in Mantoux-negative patients or in patients who are on steroids. Sir Hugh Cairns and Honor Smith<sup>7</sup> drew attention to this 18 years ago, but the lesson deserves to be borne in mind.

<sup>1</sup> Kocen, R. S., and Parsons, M., *Quarterly Journal of Medicine*, 1970, **39**, 17.

<sup>2</sup> Rich, A. R., and McCordock, H. A., *Bulletin of the Johns Hopkins Hospital*, 1933, **52**, 5.

<sup>3</sup> Taylor, K. B., Smith, H. V., and Vollum, R. L., *Journal of Neurology, Neurosurgery, and Psychiatry*, 1955, **18**, 165.

<sup>4</sup> Griffiths, D. L., Seddon, H. J., and Roaf, R., *Pott's Paraplegia*. London Oxford University Press, 1956.

<sup>5</sup> Arseni, C., and Samitca, D. C., *Brain*, 1960, **83**, 285.

<sup>6</sup> Wiseman, R. A., and Mahmood, A., *British Journal of Clinical Practice*, 1967, **21**, 13.

<sup>7</sup> Cairns, H., and Smith, H. V., in *Modern Practice in Tuberculosis*, ed. T. H. Sellors and J. L. Livingstone, vol. 2, p. 353. London, Butterworth, 1952.