

ignorant man with a hoe, his wife, and his children are a totally inadequate foundation for an enlightened state of society, a high standard of living, and elaborate social services. Much less is such a family a secure foundation for the production of goods which can pay for the import of food from the few agricultural countries still possessed of an exportable surplus. There remains the hope that in tropical countries a rise in the standard of living may result in a fall in the birth rate such as is now occurring in Western Europe and America. Even if such a fall did begin at once it would rapidly result in the Tropics also in a great increase in the number of old and non-productive people who would have to be supported by the agricultural work of their children. It is doubtful, however, whether either in Asia or in Africa the birth rate will fall within a reasonable period in the face of prohibitive religious beliefs which form a fundamental part of the indigenous cultural pattern. Yet unless the birth rate falls in relation to the death rate and the population problem is solved much talk about colonial development and welfare is, to use an American expression, "whistling in the wind."

RECENT AMERICAN WORK ON POLIOMYELITIS

The present high prevalence of poliomyelitis in this country lends special interest to reports of recent work in the U.S.A. Workers in Baltimore,¹ using the Lansing mouse-adapted strain in rhesus monkeys, have shown that after intracerebral inoculation the virus can be found in the spinal cord on the day before paralysis at the time when histological lesions are first demonstrable. The concentration of virus is maximal within the next day or two and then falls rapidly. The concentration varies with the stage of the disease rather than with the extent of paralysis. Another Baltimore paper² shows that in vaccinated monkeys with high serum antibodies there is no antibody in the cerebrospinal fluid, the anterior horn cells, or in the visual cortex. In monkeys with paralysis resulting from intracerebral inoculation the converse is observed: antibodies are present in the anterior horn cells and the medulla where the virus has multiplied, and not in the visual cortex or, except sometimes in small amounts, in cerebrospinal fluid or serum. The antibodies appear eleven to sixteen days after paralysis and persist or even increase for four or five months at least. These antibodies in susceptible parts of the central nervous system seem to be responsible for immunity, and immunity to paralysis in man may be due to their presence after invasion of the central nervous system without paralysis. Prophylactic inoculations should, however, aim at producing high serum antibody levels, as these have been proved³ to protect monkeys against intracerebral inoculations. Unfortunately the development of an effective vaccine for use in man is not yet in sight, because it would be dangerous to use the necessary large amounts of live virus and because human strains differ immunologically

from one another and from the Lansing and monkey-adapted strains. This aspect is dealt with in studies at Yale⁴ of subclinical poliomyelitis in chimpanzees in which immunity was produced to a homologous but not to a heterologous strain.

From Yale also there is an account⁵ of poliomyelitis in Japan. Large epidemics had not been noted there till 1939, and the disease was thought to be uncommon. Yet the presence of a high endemic level was shown by an average annual mortality from 1923 to 1943 of 7.6 per 100,000, which is not much lower than the figure of 8.9 for the same period in the U.S.A. The presence of virus was also shown by a high incidence of paralysis in American troops in Japan. The age incidence in Japan is highest in the 0-5 age group, as it was when large epidemics of poliomyelitis first occurred in Sweden, the U.S.A., and Australia. A marked increase in the proportion of cases in the 5-15 age group has occurred in cities in these countries since 1930. The change is well shown by figures⁶ for successive epidemics in New Haven, Connecticut. It was noted that in each epidemic the highest attack rates were in wards on the perimeter of the city and in nearby towns. No one ward was consistently attacked more severely than others, though rates were higher in wards adjacent to those heavily attacked in previous epidemics.

In a review⁷ of the work on these and other problems in the epidemiology of poliomyelitis Sabin, who has been prominent in isolating virus from faeces, declares that spread occurs from faeces and not from the pharynx. In consequence he advises the use only of those control measures which will prevent transmission of the virus from contaminated faeces. He adds that control measures are not likely to check an epidemic though they may prevent the infection of a few persons who might otherwise be paralysed. However, other investigators^{8, 9} in the U.S.A. have stressed the importance of spread from the pharynx, and a valuable discussion¹⁰ of the probable mode of spread led to the conclusions that nothing in the epidemiology of the disease is incompatible with spread from the pharynx and that spread may occur both from pharynx and faeces.

INTERPRETATION OF CHEST X RAYS

Many methods of investigation depend on personal judgments which often reveal a lack of consistency in classification between different observers and in one observer's consecutive grading of the same group. The clinical assessment of nutrition in children is a well-known example of this difficulty. Variations in judgment have also been shown in haematological and other studies. A team¹¹ working for the Veterans Association in America has recently demonstrated similar discrepancies in the assessment of x-ray films of the chest. In an attempt to determine the relative effectiveness of various techniques, 1,256 men had films taken by four different methods: "a 35 mm. photofluorogram, a 4 by 10 in. (10 by 25 cm.)

⁴ Melnick, J. L., and Horstmann, D. M., *J. exp. Med.*, 1947, **85**, 287.

⁵ Paul, J. R., *Amer. J. Hyg.*, 1947, **45**, 206.

⁶ Wenner, H. A., *Yale J. Biol. Med.*, 1947, **19**, 331.

⁷ Sabin, A. B., *J. Amer. med. Ass.*, 1947, **134**, 749.

⁸ Casey, A. E., and Fishbein, W. I., *ibid.*, 1945, **129**, 1141.

⁹ Smith, M. L., *et al.*, *ibid.*, 1945, **129**, 1150.

¹⁰ Maxcy, K. F., *Journal-Lancet*, 1944, **64**, 216.

¹¹ Birkelo, C. C., *et al.*, *J. Amer. med. Ass.*, 1947, **133**, 359.

¹ Bodian, D., and Cumberland, M. C., *Amer. J. Hyg.*, 1947, **45**, 226.

² Morgan, I. M., *ibid.*, 1947, **45**, 390.

³ Morgan, I. M., Howe, H. A., Bodian, D., *ibid.*, 1947, **45**, 379.

stereo-photofluorogram, a roentgenogram on a 14 by 17 in. (35 by 42.5 cm.) paper negative, and a conventional 14 by 17 in. celluloid film." In each case the films were taken within a few minutes of each other. They were then assessed by five experts who before the investigation had collaborated in an attempt to reach some uniformity of nomenclature.

Comparison of the interpretations of the films by the five radiologists showed varying inconsistencies. The number of the full-size celluloid films found positive for tuberculosis varied from 59 to 100; altogether 131 films were described as positive. All five agreed that the film was positive in only 27 cases. Four were in agreement on 17 films, three on 17, two on 23, and in 47 cases only one observer described the film as positive. Further individual comparisons showed that from one-third to one-half of the films described as positive by one reader were negative according to the others. The radiologist with the smallest group of 59 positives had 31, 29, 37, and 14% of his positive films described as negative by the other four. The proportion of another reader's 100 positives labelled negative by the other experts varied from 42 to 50%.

The failure of the same individual to be consistent in his judgment was even more astonishing than the variation between different radiologists. All the films were assessed for a second time at a later date by the same five readers. The proportion of first positives regarded as negative on second reading by the same expert varied from 7 to 41%, and the proportion of the second positive readings which had been called negative on a first reading ranged from 6 to 19%. The radiologist who had 59 positives originally found an additional 23 on his second assessment, but missed 4 of his own first positives.

As might be expected from the variations shown by the individuals, a comparison of the four techniques gave large differences for the same reader. The one with 59 positives on the large celluloid film called 27, 30, and 24% of these positives negative when using the other three techniques. It seemed that each of the four methods had the same degree of efficiency, since at the second assessment all five readers missed almost the same number of cases in each of the four types of film. When a majority opinion was taken there was still a considerable discrepancy. Of the full-size celluloid films 61 were positive in the opinion of three or more readers but 10, 11, and 10% of the same cases were described as negative by three or more readers when the other three types of film were used. An attempt was then made to compare the relative efficiency of the four techniques by means of a total score. Since each person in the inquiry had four films assessed by five radiologists there were 20 verdicts for each individual. Of the 1,256 cases 994 had 20 negatives; 101 had only one positive reading out of the 20; 21 cases had all 20 readings positive; and 62 had an assessment from all techniques combined of 11 or more positives. In this last group the total number of positives recorded for each of the four methods were 259, 259, 259, and 250, out of a possible 310 (5 × 62) by any one technique. This analysis suggested that all four techniques were equally likely to pick out the cases requiring further study. The small-film techniques both gave a larger proportion of over-reading. Thus out of 101 cases with only one positive 46 were read on the 35 mm., 32 on the 4 by 10 in., 13 on the paper negative, and 10 on the 14 by 17 in. celluloid film. A similar order of technique was shown by the other small positive values.

This analysis showed that the various techniques were probably equally efficient. On the full-size celluloid film some useful supplementary detail appeared in a small number of cases. The differences between interpretations

and techniques were due to a large extent to the failure of a radiologist to be consistent. Since mass radiography is being used increasingly often, these discrepancies need serious consideration if efficient screening of early cases of tuberculosis is to be attained. It seems essential that more than one radiologist should examine the films and that any case which one expert describes as positive or suggestive should be referred for further investigation.

RELIEF OF ANURIA

Many therapeutic claims based on single case records fail to withstand close analysis, either because essential data are lacking or because a multiplicity of therapeutic measures were used simultaneously. This applies particularly to measures undertaken to relieve anuria. The latter error was understandable when anuria was a desperate condition. The clinician knew that if the diagnosis had been made late he had at most three more days before a fatal outcome was to be expected. Life was too short and uncertain for art to be long. Diuretics like lactate, bicarbonate, caffeine, digitalis, sodium sulphate, and salyrgan were combined with procedures such as decapsulation, splanchnic block, or high spinal anaesthesia, often all in one unfortunate patient.

Recent advances have made it possible to view the onset of anuria more calmly. Both the artificial kidney devised by Kolff¹ of Kampen, in Holland, and the peritoneal lavage used by Fine² and his colleagues at Harvard allow us to prolong life by dialysing out of the circulating blood those substances responsible for uraemia. Neither of these methods, so far as we know, improves kidney function, although that is a possibility; they merely allow a longer period for natural or artificial restoration of renal function. As a rule, five hours on the artificial kidney will give a respite of two days. Peritoneal lavage is a slower procedure which, although technically easier, has more formidable complications, as has been pointed out by Fine himself.³ The usefulness of both procedures has been confirmed in this country and it should now be possible to attack the fundamental problem of the anuria itself.

Perhaps the most important fact we already know about anuria is that it has many and different causes and that many cases remain completely unexplained. Labels such as "reflex anuria" or "renal anoxia" are of little value. Even in anuria due to a single cause, such as mismatched transfusion, some patients will die and others will recover without, with, or despite treatment. Advocates of a particular line of therapy will always find reasons for other people's failures: this measure was applied too early or too late, too vigorously or too gently, for too short a time, or without the right sort of adjuvant treatment. Only rarely are exact criteria used. One such rarity is the record by Talbot and his colleagues⁴ of a unilateral decapsulation in a case of mismatched transfusion. The effects of this measure were observed by ureteric sampling and intravenous urography.

Criteria by which to judge the efficacy of these measures are comparatively easy to lay down when a proceeding can be carried out on one of a pair of kidneys—e.g., decapsulation, sympathectomy, or splanchnic block. They are far more difficult to establish for procedures affecting both kidneys—diuretics, spinal anaesthesia, or bilateral decapsulation. Reliance must then be placed on a close temporal relationship between the procedure and the diuresis, if any.

¹ *De kunstmatige Nier*, 1946 (abbrev. English version: *Artificial Kidney*), Kampen (Holland), J. H. Kok, N.V.

² *J. Amer. med. Ass.*, 1946, **130**, 703.

³ *Lancet*, 1947, **1**, 120.

⁴ *New Engl. J. Med.*, 1942, **226**, 228.

This involves a careful measurement of the rate of flow of the urine before and after, hourly or even half-hourly. Unless there is an immediate response, the chance that any later diuresis is due to coincidence alone becomes much greater. If failures were published, or even remembered, it seems probable that only a very small proportion of cases would ever be shown to "respond" to these measures. It would be interesting to know what this fraction is, and even more interesting to know how many of such cases recover without treatment. It seems improbable, however, that therapeutic scepticism will ever be sufficiently widespread to make this latter category large enough to treat statistically.

TOXIC EFFECTS OF MERCURIAL DIURETICS

The use of "salyrgan" as a diuretic is now widespread, and, the patent rights having expired, it has been included in the *British Pharmacopoeia* under the name of mersalyl. The official name indicates that it is a compound of mercury, and in view of the fact that mercury can be toxic it is surprising that mersalyl has maintained, in the main, so consistently good a reputation. The well-known German authority Volhard,¹ reviewing mercurial diuretics, said that for the treatment of the chronically failing heart the use of salyrgan, usually combined with strophanthin, had become indispensable; giving it weekly for many months he had never seen undesirable effects and had usually obtained entirely satisfactory results. Many similar statements have been made on its freedom from danger.

That an inherently toxic substance will eventually be found to cause toxic effects is, however, a reliable rule, and recently Oppikofer and Fehrenbach² published a paper on ulcerative mercurial stomatitis and necrosis of the jaw resulting from the use of the mercurial diuretics (salyrgan, "esidrone"). Esidrone was introduced by Ciba in 1938. The usual dose of esidrone, 2 ml., contains 44 mg. of mercury as compared with 76 mg. in 2 ml. of salyrgan. The signs of poisoning recorded by these authors are typical effects of mercury. They were observed in six patients: in five stomatitis with ulceration; in three necrosis of either the upper or the lower jaw or both; in two mercurial angina with ulceration; and in two mercurial dermatitis. In one patient salyrgan was to blame, in a second salyrgan and esidrone together, and in four patients esidrone. The doses were not excessive. The worst case was that of a man of 61, suffering from cardiac oedema, who was treated with about 20 injections of salyrgan over several months. He developed severe dermatitis and stomatitis, with necrosis of the upper jaw. When the salyrgan was stopped the dermatitis and stomatitis cleared up, but a serious jaw defect remained. Six months later the mercurial stomatitis flared up again, this time in the lower jaw, and he bled from the lingual artery.

The Swiss authors of this paper evidently know nothing of BAL (dimercaptopropanol) which was introduced by Peters, Stocken, and Thompson³ during the war as an antidote to arsenical poisoning, and which has been shown⁴ to be equally effective in mercurial poisoning. BAL is not yet generally available, though it has been supplied to V.D. clinics on application to the Medical Research Council. It will soon be in commercial production. BAL combines with mercury in the body and the combination is rapidly excreted. A patient receiving mersalyl will show, as the earliest sign of poisoning, excessive salivation. When

this occurs mersalyl should be withheld and BAL given by intramuscular injection. It is interesting to note that even the acute forms of mercury poisoning can be arrested by BAL. Long and Farah⁵ have shown that the sudden failure of the heart which occasionally occurs when mersalyl is given intravenously can be overcome by the intravenous injection of BAL, but recovery of course occurs only when BAL is given without delay. Acute heart failure from mersalyl very rarely occurs if it is given by intramuscular injection. Since the diuretic effect is intended to be of several hours' duration at least, this route is the more rational.

BLOOD GRAVITY AND HAEMOGLOBIN

The need for the control of intravenous infusion in war injuries led the United States Navy Research Unit at the Rockefeller Institute to develop the copper sulphate method for measuring the specific gravities of blood and plasma.⁶ A drop of blood in a copper sulphate solution becomes encased in copper proteinate—and so remains discrete, and sinks or swims according to whether its specific gravity is greater or less than that of the solution. If drops of blood are let fall into a series of copper sulphate solutions of known gravity the drops will neither rise nor fall in the solution which has the same gravity as the blood. The specific gravity of plasma or serum is affected only by variations in the protein content, and the total plasma or serum proteins can be estimated as accurately by the copper sulphate specific gravity technique as by any other routine method. The gravity of whole blood depends on the plasma protein level and the number and specific gravity of the erythrocytes. If we assume a constant value for the erythrocyte gravity we can calculate, from the whole blood and plasma gravities, the ratio of red-cell volume to plasma volume—the ratio more laboriously but more accurately measured by the haematocrit. If we further assume a normal mean corpuscular haemoglobin concentration then we can calculate the haemoglobin level.

Since it is doubtful whether these calculations offer any substantial advantage over a simple haemoglobin determination in the treatment of shock and burns, the copper sulphate method has established itself principally as an accurate technique for the estimation of the total plasma proteins. There are occasions, however, when use can be made of the fairly close correlation between the whole blood gravity and the haemoglobin level. If we assume normal values for the plasma proteins, the erythrocyte gravity, and the mean corpuscular haemoglobin concentration, then the haemoglobin level can be calculated directly from the whole blood gravity, with an error of about $\pm 10\%$. This is too great an error for individual haemoglobin estimations, but if we wish simply to pick out the anaemic members of a large group then the ease and rapidity of the method outweigh its inaccuracy.

The New York Blood Donor Centre used this method to "screen" prospective donors.⁷ A drop of blood from the finger was allowed to fall into a copper sulphate solution of gravity 1.052; if the blood sank the donor was accepted; if it floated he or she was assumed to be anaemic, with a haemoglobin level under 12.3 g. Only 4% of donors were wrongly classified by this method. Hynes and Lehmann⁸ made a similar application of the method. They showed that the blood gravity and haemoglobin were related more

⁵ *Science*, 1946, **104**, 220.

⁶ Phillips, R. A., Van Slyke, D. D., Dole, V. P., Emerson, K., Hamilton, P. B., and Archibald, R. M., *Copper Sulphate Method for Measuring Specific Gravities of Whole Blood and Plasma*. (Josiah Macy, jun., Foundation, New York, 1945.)

⁷ *J. Lab. clin. Med.*, 1946, **31**, 40.

⁸ *J. Physiol.*, 1946, **104**, 305.

¹ Bergmann, G. von, and Staehelin, R., *Handbuch der Inneren Medizin*, **6**, 361. Berlin, 1931.

² *Schweiz. med. Wschr.*, 1946, **76**, 983.

³ *Nature*, 1945, **158**, 616.

⁴ *J. Pharmacol.*, 1946, **87**, Suppl. 85.

accurately by an empirical curve than by the original linear calculation; only 3% of 270 men were wrongly classified as above or below a haemoglobin level of 11 g.

In practice, if further investigation of anaemic subjects is intended, it is wise to choose a copper sulphate solution corresponding to a haemoglobin level 1 g. above the chosen limit of anaemia. Then practically no anaemic individuals will be missed, though there will be a corresponding increase in normal subjects classified as anaemic.

TRAINING CLINICAL PATHOLOGISTS

What are the functions of a clinical pathologist? When this topic was debated in our correspondence columns a year ago attention was chiefly paid to diagnostic laboratory procedures, but, as the Association of Clinical Pathologists points out in a recent report, a function of increasing importance is "the control of treatments of various disorders whose progress can most accurately be assessed by laboratory methods." It emphasizes that a clinical pathologist should have a sound clinical training, including higher qualifications in medicine, as well as a wide experience of laboratory technique. The Hospital Surveys carried out for the Ministry of Health recognized the essential part that this specialty must play in a national hospital service, and there was, as Dyke¹ said commenting on them, "general agreement that satisfactory results cannot be attained by mere isolated examination and report on specimens, but only by direct consultation between practitioner and pathologist."

The Association of Clinical Pathologists appointed a committee in January of this year to consider the training and definition of consultants and specialists in clinical pathology. Its members were E. N. Allott (chairman), S. C. Dyke, R. W. Fairbrother, J. G. Greenfield, and W. H. McMenemy. The committee recommends that the five years after qualification should be devoted to gaining further clinical experience (one year), working in a university department (one year), and working in a department of clinical pathology (two years). In the remaining year the student should extend his experience as he wishes. The object of working in a university department is to train the student in scientific method and to introduce him to an atmosphere where research is being vigorously pursued; the committee suggests that students should be encouraged to take a diploma in bacteriology or in clinical pathology. While working in a department of clinical pathology in a large hospital or a group laboratory the student should receive training in all branches of pathology—a study that should include haematology, bacteriology, chemistry, and morbid anatomy. In this connexion the committee recommends that a special committee be set up to approve those laboratories suitable for this training. Those students who have obtained a first- or second-class science degree—for example, in physiology or chemistry—or a doctorate of philosophy should be eligible for recognition as specialists four instead of five years after registration.

The committee recognizes that these criteria cannot necessarily be applied to existing clinical pathologists or to some of those in training. It advocates, therefore, that at present recognized specialists should have been registered for a minimum of five years and have had at least four years' laboratory experience. They should also hold a higher medical or scientific qualification, or have contributed to the advance of medical or scientific knowledge. In accordance with a decision of the Royal College of Physicians the committee does not think that a register of

specialists in clinical pathology should be compiled. Discussing the financial support that these years of training necessitate and whose lack often debars poorer students from undertaking them, the committee quotes the recommendation of the Royal College of Physicians Committee on Neurology that suitable candidates for the specialty should be supported by scholarships, Government grants, or otherwise.

CARE OF THE AGED

The Nuffield Foundation is an outstanding example of that modern form of charity whereby help is made available at the point where it is most needed, instead of being frittered away in small sums that keep the wolf from the door only to fail when he jumps through the window. Even our most rigorous planners acknowledge that voluntary aid is desirable, and will remain so, if life is to be not merely sustained but made worth living. The Foundation's latest venture is to sponsor, in association with the Lord Mayor of London's National Air Raid Distress Fund, a National Corporation for the Care of Old People, under the chairmanship of Sir George Wilkinson, Bart., and to provide it in the early years with the sum of £500,000. The offices will be at 9, Mecklenburgh Square, London, W.C.1. Sir William Goodenough, speaking at the inauguration of the Corporation on July 28, explained that its primary function is to co-ordinate the many agencies that already exist for the benefit of old people. It will not assist individuals but will make grants or loans for schemes for old people's welfare, maintain an advisory service, establish and demand desirable standards for organizations applying to it for aid, and undertake research. Moreover, by offering grants or loans, it will take the initiative in areas where welfare for the old is lacking. The Corporation will be a complementary partner of the National Old People's Welfare Committee.

As the Rowntree Report¹ pointed out, the old more often suffer from loneliness than from dire poverty. The Nuffield Foundation has taken account of this in its 1947 Report,² and emphasizes that the community must not become stratified into large groups: provision for the old, in the interests of both old and young, must "be so planned that it is integrated into the life of younger sections of the community so as not only to enliven the surroundings of the older generations but also to enable the young to contribute in awareness and in activity to the welfare of the old." It would nevertheless be regrettable if widespread public arrangements for their welfare should diminish the sense of family responsibility to look after elderly relatives. The Report recognizes that many more suitable dwellings should be built for the old rather than experiments carried out on types of housing, of which enough have already been done. Discussing the dwellings themselves, the B.M.A. Committee on the Care and Treatment of the Elderly and Infirm³ stressed that houses for the elderly should be decorative, situated where the residents have previously lived so that they may keep in touch with their friends, near churches and shops and places of entertainment—not "machines for living in," to use a phrase popularized by Le Corbusier, but homes. The Ministry of Health, too, has impressed on local authorities this aspect of housing the old. Voluntary aid is perhaps essential to provide this distinction, and the Corporation is well fitted to the task.

¹ *Old People*. Report of a Survey Committee on the Problems of Ageing and the Care of Old People, under the chairmanship of B. Seebohm Rowntree. Geoffrey Cumberlege, London, 1947.

² The Nuffield Foundation: Report of the Trustees for the year ending March 31, 1947. The University Press, Oxford, 1947.

³ *British Medical Journal (Supplement)*, 1947, 1, 133.