system of government and who had somewhat unusual views on the preservation of the health of the body politic. This same doctor, having noted that those in power are often troubled with short and weak memories, proposed that "whoever attended a first minister, after having told his business with the utmost brevity, and in the plainest words, should, at his departure, give the said minister a tweak by the nose, or a kick in the belly, or tread on his corns, or lug him thrice by both ears, or run a pin into his body, or pinch his arms black and blue, to prevent forgetfulness."

REFERENCES

- ¹ The Social Services. Walter Hagenbuch. *London and Cambridge Economic Service*. Vol. 29. Bulletin 3, p. 74.
- ² Fifteenth Annual Report of the Registrar-General, 1852. London.
- ³ Farr, Wm. Letter to the Registrar-General on the Causes of Death in England in 1852. Appendix to 15th Annual Report of Registrar-General. London.
- ⁴ Quoted by Sir John Simon in his 6th Annual Report to the Privy Council, 1863. London.
- ⁵ London County Council. Annual Report of the County Medical Officer for 1950, p. 1.
- ⁶ *Ibid.*, p. 124.
- ⁷ Jameson and Parkinson. *Synopsis of Hygiene*, 10th ed., by L. Roberts, p. 7, 1952. London.
- ⁸ The British Health Services. P.E.P., 1937, p. 263. London.
- ⁹ An address delivered at the Annual General Meeting of the Institute of Almoners. *The Almoner*, 1952, 5, 3.
- ¹⁰ Central Health Services Council. Report on Co-operation between Hospital, Local Authority, and General Practitioner Services, 1952. H.M.S.O., London.
- ¹¹ Macaulay, *History of England*, ch. xi.

RECENT ADVANCES IN ACTIVE IMMUNIZATION

(DIPHTHERIA, WHOOPING-COUGH, TUBERCULOSIS)*

BY

H. J. PARISH, M.D., F.R.C.P.Ed., D.P.H.

(From the Wellcome Research Laboratories, Beckenham, Kent)

A discussion on active immunization enables us to review advances made in the laboratories of many countries since the war, and also to indicate current trends likely to prove useful to the medical practitioner—surely a main function of the Annual Meetings of the British and Irish Medical Associations. It must be remembered, however, that there is a long incubation period between the conclusion of any new work and the writing of a paper on the subject. Following this there is a long latent period before the article appears in print. Any summary of advances in active immunization cannot ever be up to date, and any statement made to-day may be contradicted to-morrow.

Since chemotherapy and antibiotics are being employed with varying success in the treatment of many diseases, inquiries are naturally made about the future of specific means of control (toxoids and vaccines). In spite of the progress of chemotherapy, immunology has still a very important part to play in prevention and treatment, and there is a need for further research on antigens and methods of using them effectively.

Diphtheria

Since the launching of the national immunization campaign by the Ministry of Health, London, in 1940, the reduction in the toll of this disease in England and Wales has been dramatic. In 1951 diphtheria deaths numbered only 34 (provisional figure) and corrected notifications 699, compared with approximately 3,000 deaths and 55,000 to 60,000 notifications per annum just before the second world

*Read in opening a discussion in the Section of Pathology and Bacteriology at the Joint Annual Meeting of the British Medical Association and the Irish Medical Association, Dublin, 1952.

war. Fifty years ago there were nearly 10,000 deaths per annum. Moreover, in the past, about 10% of infants might have been expected to suffer an attack of diphtheria and 1% (10% of cases) to die from it (*Medical Officer*, 1951). Where inoculation has been fully practised the toll has been reduced to about 1% of what it was. More convincing evidence of the value of immunization is that the diphtheria notification rate was three times higher and the fatality rate seven times higher over the three years 1945, 1946, and 1947 among non-immunized than among immunized children aged under 15 (Logan, 1952). The chance of a non-immunized child under 15 dying of diphtheria was 22 times as great as that of an immunized child in the same community. These magnificent achievements have not received the attention they merit, because preventive medicine is largely impersonal. The benefit conferred is not appreciated consciously by the person whose life is saved, nor indeed by anyone else. Yet the cost is relatively insignificant both in money and in the trouble involved.

I think we should be careful not to ascribe the improvements in the diphtheria position solely to immunization. As is well recognized, scarlet fever and other acute infections have shown a decline in mortality during the last 50 years, although there has been no comparable immunization campaign for their control. Other factors are at work, including, in diphtheria, a possible change in the invasiveness of the causal bacillus. There must be no slackening in our propaganda, but rather an intensification, for there are already in different countries too many susceptible persons, presumably prone to attack by the "enterprising" virulent bacillus we used to know. In a recent review by McGuinness (1952) 30 to 50% of American adults are mentioned as being susceptible. Barr, Glenny, and Parish (1951) examined the diphtheria antitoxin content of 100 samples of cord blood from each of 15 districts of the British Isles; in 10 of the groups, 30 to 59% of the samples contained no detectable antitoxin (under 0.001 unit per ml.). It is obvious that the decline of attendance last year at British clinics must not be accepted with complacency, but be countered by really forceful official propaganda. Mothers who have lost their fear of diphtheria as a deadly illness must not be allowed to remain apathetic.

Not only are there very few cases of diphtheria to-day, but also apparently very few carriers in the general population. Immunization has not increased the number of carriers, as was once thought possible. Thus a paper from Leeds (Bradshaw *et al.*, 1952) stated that no carriers were found in the examination of 6,675 swabs from a highly immunized child community. Other evidence, too, suggests that carrier rates fall along with diphtheria morbidity as a result of immunization. This means that, to-day, immunity to diphtheria is less likely to be maintained at a safe level as a result of subinfecting doses of toxigenic diphtheria bacilli. These are so infrequent that we can no longer expect any "boosting" of circulating antitoxic titres from natural immunization. Artificial immunization has therefore taken on an important function, and it must be continued vigorously, endeavouring to conform to good immunological procedures. I have presented the essential principles in convenient form elsewhere (Parish, 1951).

Logan (1952) has stated that the eradication of diphtheria as an indigenous disease in England and Wales can be foreseen as a very real possibility within the next few years. Nevertheless, let us not be overconfident, since the immunity state of the population is disconcertingly low in many areas.

The Prophylactics

All the preparations in use in the world to-day have toxoid or formol-toxoid (French=anatoxine) as their basis; the original highly dangerous toxin has been modified and rendered harmless with formaldehyde, while its capacity to stimulate the production of antitoxin is retained. The fact that unmodified toxin is never used is important, since it precludes any possibility of accident of the type encountered when toxin-antitoxin mixtures were favoured in the U.S.A.

and elsewhere. Toxoid was used for the active immunization of horses by Glenny and by Loewenstein in 1904 (O'Brien, 1925); it was *not* discovered by Ramon in 1923, as is sometimes alleged, although Ramon was instrumental in having it used on a very large scale for the immunization of French children and soldiers. To-day toxoid is still used on the Continent and in Canada, but prophylactics derived from it are preferred in Great Britain and Ireland. Alum-precipitated toxoid and toxoid adsorbed on mineral carriers give much better antitoxin responses than the fluid antigen.

A.P.T. (alum-precipitated toxoid) has been the prophylactic most used in Great Britain since 1940. I have emphasized that our immunization schemes must be thorough. Better immunity follows the injection of large doses, and there seems to be no good reason why amounts of less than 0.5 ml. (25 Lf) should not be injected into infants. It is worth noting that young children tolerate 0.5 ml. extremely well, although older children and adults sometimes suffer reaction, local and general.

Barr, Glenny, and Randall (1949, 1950) studied the rate of loss of maternally transmitted diphtheria antitoxin in young babies, and found that those with less than 0.04 unit of antitoxin per ml. of their serum could be immunized successfully with two doses, each of 0.5 ml., of A.P.T. These authors also suggested the routine immunization of infants with A.P.T. at 3, 6, and 18 months. In general, the larger the dose used the less the possible interference from maternal antitoxin and the better the response. In younger and lighter babies more antigen was being injected per kg., a point in favour of early immunization. The case for early immunization has received much attention recently in several countries, and I shall refer to it again in the section dealing with combined immunization.

In order to give as good an immunity as possible in routine work it is suggested that: (1) The amounts of A.P.T. injected should always be 0.5 ml. except in older children and adults, in whom 0.2 ml. may be substituted as a preliminary "detector dose" of reactions at the start of the course. As a general rule, a second and final injection of 0.5 ml. is accepted as adequate. (2) In the present state of our knowledge, a single boosting dose at the time of entry to school (Cruickshank, 1952) may be enough for most children who have had a primary course of two well-spaced doses. However, many authorities prefer to give a second boosting dose a few years later. Perhaps a better scheme is to give one boosting dose at 18 months and a second at 4 to 5 years, instead of at 4 years and at 10 years, as is generally advised at present.

T.A.F. (toxoid-antitoxin floccules), which is a weaker antigen than A.P.T., is still used for immunizing adults or those believed to be sensitive to bacillary protein and likely to suffer reaction.

P.T.A.P. (purified toxoid aluminium phosphate precipitated) is used in the same way as A.P.T. It is still undergoing clinical trial. The main point about it is that it contains far less bacillary protein than A.P.T., but it is not known whether absence of bacillary protein is an advantage or a disadvantage in diphtheria prophylaxis.

F.T. (formol-toxoid) has been used both as a crude and as a "pure" or purified preparation. Much research has been directed towards the improvement of toxoid as a basis of all prophylactics. Although so-called "pure" toxoids have been prepared, Pope *et al.* (1951) have found many antigens in them; the composition of diphtheria antigens is more complex than was formerly realized.

Whooping-cough

This is one of the most prevalent and certainly the most lethal of the acute specific infections of childhood. In England and Wales, 9,401 deaths occurred from whooping-cough in the past ten years (Cockburn, 1951). Death is rare in children over 4 years of age; more than 50% of all the deaths are in children under 1 year. Whooping-cough also gives rise to much permanent lung damage from atelectasis and bronchiectasis.

As a clinical attack of whooping-cough gives a fairly solid immunity, successful vaccination has always appeared to be an attainable goal, even in the absence of a simple and reliable laboratory test of antigenicity. Nevertheless, until recently the voluminous literature was so contradictory that scepticism was a common and justifiable attitude to the whole question. But the very persistence of the claims, mainly American, demanded a more critical and better controlled appraisal than this important product had hitherto received.

The British Medical Research Council appointed a committee to go into the matter in 1944, and its interim report (M.R.C., 1951) has shown clearly and conclusively that good vaccines can be prepared. Altogether 7,558 children aged 6 to 18 months were divided into two groups distributed among five different areas. Half the children in the trials received three doses at monthly intervals of various whooping-cough vaccines of British and American origin, and half were inoculated with "anticatarrhal" vaccine as controls. A nurse investigator visited each child at frequent intervals for two to three years, and neither parents nor observers knew to which group each child had been allocated. A total of 3,757 children in the control group produced 687 cases of pertussis by the end of the inquiry, and 3,801 vaccinated children produced 149 cases. The attack rates per thousand child-months of observation were 6.72 among the unvaccinated and 1.45 among the vaccinated, giving a reduction of 78% in the incidence of the disease. Among children exposed to pertussis in their own homes the attack rates were 87.3% of the unvaccinated and 18.2% of the vaccinated group. Further, the cases occurring in the vaccinated were on the average less severe and of shorter duration.

Of the five vaccines tested, two prepared at the Michigan Department of Health were much better than the others, the attack rates in "home exposures" being only 7.3 and 8.9% amongst the vaccinated. Somewhat similar vaccines have now been prepared in Great Britain, and are being studied in laboratories by the Kendrick mouse intracerebral test, and also in various clinics, with a view to determining the value of this novel but promising method of laboratory assay. Field trials of whooping-cough vaccine take a long time, but eventually enough evidence may be produced to justify a national campaign similar to the one introduced for diphtheria immunization by the Ministry of Health, London, in 1940.

In view of the severity and prevalence of whooping-cough in children under 1 year of age, early protection is obviously desirable. Many authorities, particularly in the U.S.A., recommend that the first injection of the course should be given at 2 to 3 months of age, followed by two further injections at monthly intervals. There is no general agreement about the frequency of boosting doses, but until more is known about the reliability of commercial vaccines, one such stimulus per annum till the child is aged 3 to 4 years cannot be regarded as excessive. Moreover, after known close exposures a further dose of vaccine may be advisable.

It is sometimes recommended that mothers should be actively immunized against whooping-cough in the early months of pregnancy. Although high agglutination titres can be demonstrated both in maternal and in cord-blood sera, the protective titres may not be high. At this stage little reliance can be placed on the immunization of mothers as a means of control.

Alum-precipitated vaccines have not hitherto been employed in the British Medical Research Council investigations, but they have been preferred by many workers in the U.S.A., as the alum may possibly have an adjuvant effect in certain types of preparation.

A modified Hornibrook liquid medium (casein hydrolysate, starch, etc.) promises to be satisfactory for the preparation of whooping-cough vaccines on a large scale. The processes of manufacture are simplified, and preliminary reports indicate that the vaccines so produced may be highly potent antigens.

An interesting American development is active immunization with live vaccine (Winter *et al.*, 1952), in an attempt to reproduce artificially the better and more lasting protection conferred by an attack of the disease. The live antigen proved superior to killed vaccine in mouse-protection tests, and its use in human subjects is now under investigation. As *Haemophilus pertussis* is not invasive, it should not cause the actual disease when introduced by any route other than the respiratory tract. The method should therefore not entail undue risk.

Complications of Ordinary Vaccination.—In young children reactions are usually slight, although rather more than after diphtheria prophylactic A.P.T. So-called encephalopathies, manifested by convulsions and other serious nervous symptoms appearing within a few hours or days of inoculation, are rare and may be due to some acquired sensitivity or possibly, in certain cases, to a cerebral vascular accident. As a precaution, any child with a personal or family history of convulsions, and, secondly, any child who has recently had, or is likely to have soon as a result of close contact, any respiratory or other infection should be excluded from vaccination. The association of pertussis inoculations with paralytic poliomyelitis in the inoculated limb is discussed below.

Combined Immunization

The modern trend favours combined immunization in order to reduce the number of inoculations. Moreover, the antigenic response to certain antigens seems to be enhanced.

Diphtheria-pertussis and diphtheria-tetanus-pertussis prophylactics are used on a large scale in the U.S.A. for the immunization of young children. Diphtheria-pertussis prophylactic seems to be less used than formerly in Great Britain on account of the fear of associated poliomyelitis. This combined prophylactic is supposed by many to involve an exceptional risk of the "double event," although the special case against it is still unproved. In this connexion Cockburn (1951) favours the development of combined antigens which do not contain alum, as they should cause less local trauma than other types. A committee is now inquiring into the relationship of paralytic poliomyelitis and inoculations of all kinds. Until the report is published the sensible course is probably to postpone all preventive inoculations during epidemic periods, but the decision must obviously rest with the local health authorities, who have to assess the relative risks of poliomyelitis and of the various infections that may well recur if too much damage is done to the immunization campaigns in the district. Alarmist press reports and correspondence may also have done harm, particularly to the diphtheria campaign, by undue publicity and magnification of the risks.

In view of the high incidence of whooping-cough in the first year of life, some authorities have suggested that the immunizing course of diphtheria-pertussis prophylactic should be begun at 2 to 3 months, as in the case of pertussis vaccine alone. Three doses are generally given at intervals of not less than four weeks, followed by a fourth dose in the second half of the first year of life. There is considerable variation in procedure. Boosting doses may be given at the age of 2 to 3 years and again at 4 to 5 years. Reactions are not worse than would be expected from those observed after each constituent given separately, which means that they are usually negligible in young children.

In concluding this section, I think more attention should be paid to immunization against tetanus, as triple combined prophylactics are feasible. Tetanus toxoid is one of the most effective prophylactics yet developed, and causes so little reaction on injection that immunity is obtained at negligible cost and inconvenience. Many American workers believe that everyone should be actively immunized against tetanus (McGuinness, 1952). Combined antigens—diphtheria, pertussis, and tetanus—have much to recommend them for young children.

Typhoid-paratyphoid vaccine in conjunction with tetanus toxoid (T.A.B.T.) has been used for many years for the Canadian Armed Forces. A recent modification has been the addition of a small amount of diphtheria prophylactic—namely, toxoid adsorbed on aluminium phosphate—following the method of Holt. Three injections of 1 ml. each of the new prophylactic, T.A.B.T.D., are given at monthly intervals, and the indications are that the diphtheria antigen (4 Lf per ml.) does not appreciably increase the amount of reaction (Sellers *et al.*, 1951).

Tuberculosis

As is well known, B.C.G. (Calmette-Guérin bacillus) and vole-bacillus vaccines consist of living bacteria and produce some degree of active immunity in guinea-pigs and calves in controlled experiments. There is also less well-controlled evidence that they protect man, for whom killed vaccines were found to be ineffective.

B.C.G.

In England and Wales the B.C.G. campaign was begun in October, 1949, using the strain of B.C.G. maintained at Copenhagen (Symposium, 1951). Vaccination was offered to hospital nursing staff, medical students, and contacts of known cases of tuberculosis. The intradermal route of administration was employed. Tuberculin-testing was regarded as an essential preliminary; only those persons who were Mantoux-negative on two tests spaced by six weeks were vaccinated. After segregation for six weeks in the case of adults, or for eight to twelve weeks in the case of children, a third tuberculin test was made. A positive reaction ("Mantoux-conversion") was regarded as an indication that immunity had resulted.

The mortality from tuberculosis has fallen in a number of countries, but there is no scientific proof that it is due to B.C.G. (see, for example, Partenheimer, 1951). In some of these countries, notably Iceland, where the fall has been very great, B.C.G. has not been used at all. The Medical Research Council, London, hopes to get an answer to the problem of the value of B.C.G. within three years.

In Ireland there has been much more enthusiasm for B.C.G. vaccination than in Great Britain. A most energetic attack on the tuberculosis problem at its source has been made over wide districts—for example, in Dublin (Price, 1949) and in County Sligo (Burke, 1951). This magnificent and praiseworthy effort continues.

In the U.S.A. Aronson (1948) reported 55 deaths among approximately 1,500 vaccinated North American Indians; six of these deaths were due to tuberculosis. In the control group, exposed equally to subsequent infection, there were 109 deaths, 53 of which were due to tuberculosis. These results attracted much attention, although they may not be applicable to more civilized communities where genetic immunity to tuberculosis is higher and the risk of infection usually less. Later, Myers (1951) argued strongly against the use of B.C.G. This criticism from a leading American authority raised once again regrets that a controlled study, involving the injection of alternate subjects, was not carried out in man in the early days of B.C.G. vaccination in France. Controlled tests in cattle in the U.S.A. did not show any practical justification for the use of B.C.G. Myers also attacked the Scandinavian claims by pointing out that medical students and nurses who are tuberculin-positive on entry have already passed through the stage of "allergic manifestations." From his own early experience, a small proportion of children and adults had "fever, erythema nodosum, pleurisy, enlargement of hilar structures, and small infiltrates in the lungs"; when these primary complexes subsided the patients appeared well, except in rare instances.

To illustrate his thesis of the comparable risk of tuberculin-positive and tuberculin-negative subjects, he exemplified 160 tuberculin-positive medical students and 145 students tuberculin-negative on entry who later became positive. Of the former group, 3.1% developed reinfection lesions, and

of the latter group 9.6% developed demonstrable lesions. But when the 9.6% of students were analysed further, 6.2% were regarded as primary complexes and pleurisy and only 3.4% as reinfection lesions, a figure similar to the 3.1% of the first group.

The point was also made that B.C.G. has not been proved to be harmless; there have been a number of reports about "Calmette" abscesses and even of pulmonary infiltration. However, Myers's main argument was that there is no justification for taking decreasing mortality as the criterion of the protective power of B.C.G., since similar reductions have been noted in unvaccinated communities. Thus the tuberculosis situations in Denmark and Minnesota showed comparable declines in mortality in recent years, although B.C.G. was used only in Denmark. Myers felt that conventional methods, rather than B.C.G., should get the credit for the improvements in Denmark, as they do in Minnesota. I have already referred to the decline in tuberculosis mortality in Iceland, which was even greater than in Denmark and took place without any assistance from B.C.G.

In favour of B.C.G. are numerous experiments in animals, which show that immunization with the vaccine retards the development of tuberculosis following later injection of virulent tubercle bacilli, and thus results in a more chronic type of infection. This should afford a basis for the hope that in man a resistance should be set up of sufficient duration to support the defences of the body during the danger period when natural infection is taking place. However, Myers maintains that there is no evidence of the development of effective immunity even after an attack of tuberculosis from which a patient has apparently recovered. According to him, parallelism between hypersensitivity and acquired resistance is non-existent: allergic tissues are a prerequisite to the development of the more destructive forms of tuberculosis, the bacilli which were held up temporarily being widely disseminated.

The intradermal method of administration has been most used in Great Britain and Ireland and in Sweden and Denmark, while multiple puncture (with a Hagedorn needle or other instrument) and scarification have been preferred in Norway and France respectively. Newborn infants used to be given B.C.G. by mouth, but this technique is now obsolete. Intradermal vaccination in the deltoid region as soon after birth as possible has recently been employed by Gaisford and Griffiths (1951).

Much attention has been given recently to the method of preparation of the vaccine. "Liquid vaccine," which is the type ordinarily used in Great Britain and Ireland and in Scandinavia, has a very short life—only ten days or so from the date of preparation. (This and other traditional concepts about B.C.G. vaccine and vaccination have been challenged recently by Palmer (1952), of the Tuberculosis Research Office, W.H.O.) Freeze-dried vaccine should retain full viability and immunizing efficiency for many months. The workers at the Pasteur Institute, Paris, have been outstanding in developing a dry vaccine.

My own views in this difficult field of vaccination against tuberculosis may be summarized as follows. While the value of B.C.G. in man has not been proved, it is sounder preventive medicine to produce primary allergic complexes with a living attenuated vaccine, even if its complete innocuousness is occasionally in doubt, than to risk the potentially dangerous manifestations that may result from random natural infection with virulent bacilli. The essence of all vaccination procedures is to produce some immunity with antigens, living or dead, that are safer than an attack of the natural disease. One recalls that, in the case of smallpox, variolation was replaced by vaccination, and that Pasteur's attenuated virus is used in the prevention of rabies. But it is also noteworthy that in the attack on tuberculosis "fundamental control measures" have often produced considerable falls in mortality without any part being played by B.C.G. At best, B.C.G. must be regarded as an adjunct to, and not as a substitute for, precautions introduced to prevent fre-

quent or massive exposure to infection. Unfortunately in many countries to-day the injection of B.C.G. is the only measure of control which is practicable.

Wells's Vole Bacillus (Living)

This is the only tuberculosis vaccine which competes at all with B.C.G. It consists of a culture of a strain of murine tubercle bacillus, and has the advantage over B.C.G., an artificial laboratory product, that it is already stabilized in its virulence for man and cattle. Attenuation from prolonged and repeated subculturing is thus unnecessary. Although some results in guinea-pigs, cattle, and man are encouraging, it is unlikely that Wells's vaccine will ever oust B.C.G., or even offer a serious challenge to it, if only because B.C.G. is already well established.

REFERENCES

- Aronson, J. D. (1948). *Amer. Rev. Tuberc.*, **58**, 255.
 Barr, M., Glenn, A. T., and Parish, H. J. (1951). *Lancet*, **1**, 713.
 ——— and Randall, K. J. (1949). *Ibid.*, **2**, 324.
 ——— (1950). *Ibid.*, **1**, 6.
 Bradshaw, D. B., Dixon, C. W., Mawson, F. M., Turner, G. H., and Zinnemann, K. S. (1952). *Ibid.*, **1**, 558.
 Burke, F. J. (1951). *British Medical Journal*, **2**, 887.
 Cockburn, W. C. (1951). *Practitioner*, **167**, 232.
 Cruickshank, R. (1952). *British Medical Journal*, **1**, 212, 268.
 Gaisford, W., and Griffiths, M. (1951). *Ibid.*, **2**, 702.
 Logan, W. P. D. (1952). *Monthly Bull. Minkst. Hlth, Lond.*, **11**, 50.
 McGuinness, A. C. (1952). *J. Amer. med. Ass.*, **148**, 261.
Medical Officer, 1951, **85**, 256.
Medical Research Council (1951). *British Medical Journal*, **1**, 1463.
 Myers, J. A. (1951). *J. Amer. med. Ass.*, **146**, 1492.
 O'Brien, R. A. (1925). *Lancet*, **1**, 102.
 Palmer, C. E. (1952). *Ibid.*, **1**, 935.
 Parish, H. J. (1951). *Bacterial and Virus Diseases: Antisera, Toxoids, Vaccines and Tuberculin in Prophylaxis and Treatment*, 2nd ed. Livingstone, Edinburgh.
 Parteneimer, R. C. (1951). *New Engl. J. Med.*, **245**, 496.
 Pope, C. G., Stevens, M. F., Caspary, E. A., and Fenton, E. L. (1951). *Brit. J. exp. Path.*, **32**, 246.
 Price, D. S. (1949). *Tubercle*, **30**, 11.
 Sellers, A. H., Caldicott, G. D., Waters, G. G., and MacQuarrie, M. J. (1951). *Canad. J. Publ. Hlth*, **42**, 269.
 Symposium on B.C.G. Vaccination in England and Wales (Smith, N., Heaf, F. R. G., and Daniels, M.). *Publ. Hlth*, 1951, **64**, 187.
 Winter, J. L., Doyle, E. F., and Brown, C. R. (1952). *Proc. Soc. exp. Biol., N.Y.*, **79**, 122.

FOUR CASES OF OBSTRUCTION AT THE DUODENO-JEJUNAL JUNCTION

BY

F. A. R. STAMMERS, C.B.E., Ch.M., F.R.C.S.

Professor of Surgery, University of Birmingham

Unusual cases tend to come in runs, and sometimes present such similar features as to enable those who have encountered them to suggest the diagnosis in subsequent cases with reasonable certainty. During the past year four such cases have come our way—namely, obstruction at or near the duodeno-jejunal junction resulting from narrowing by growth. Two were caused by primary carcinoma of the duodenum, one followed infiltration by carcinoma of the body of the pancreas, and one followed infiltration by some adenopathy of adjacent glands. Each case presented points so strikingly alike that the syndrome could be recognized as pointing to some stenosis at or just beyond the junction.

Case 1

A minister of religion aged 39, a married man with one child, had been in robust health until six weeks previously. He was then on holiday, during which he began to suffer epigastric pain some 10–15 minutes after meals. It lasted about an hour, was unrelieved by alkalis, and did not radiate in any direction. Within a few days he began to vomit copious amounts of dark-green, watery, bitter-tasting fluid. This vomiting was quite unrelated to food, and he declared that pints of fluid just flowed from him. He was put on a milk diet, and remained on it until admission to hospital.