possible to say which of the differences were responsible for the widely divergent results.

The field studies showed that in the second series three vaccines (V9, V10, and V12) made in this country from strains of *H. pertussis* isolated here were as effective as the reference vaccine (V8) made with American strains and supplied by the Michigan Department of Health, and that the vaccine prepared by the State of New York Department of Health (V11) from the same American strains as the reference vaccine, but grown in liquid medium, was, in a preliminary trial, also as effective as the reference vaccine.

At the same time as the field trials were in progress, laboratory tests were made in which the vaccines were extensively tested for their ability to protect mice against intracerebral pertussis infection. Some of the vaccines were tested for their ability to produce agglutinin in mice, and sera from a number of vaccinated children were titrated for agglutinin.

There was a correlation between protection in children and three laboratory tests: (a) protection of mice against intracerebral infection with *H. pertussis*, (b) production of specific agglutinin in mice, and (c) production of specific agglutinin in children. Though the three laboratory tests gave results parallel with those obtained in the field, it does not necessarily follow that the laboratory tests measure directly the factor or factors responsible for the production of immunity in children. Pillemer and his colleagues (1954) have prepared from *H. pertussis* an antigenic fraction which protects mice against intracerebral infection, but which produces a very poor agglutinin response in mice (Evans and Perkins, 1955). The protective potency of this fraction in children is being tested at present in Liverpool and preliminary results suggest that it is giving protection. The mouse-agglutinin-production test therefore may not be a reliable guide to the value of all vaccines in children. Agglutinin production in children has been accepted by some workers as evidence of protective potency, and the tests reported here support this conclusion. Production of agglutinin, however, is only one of the properties of *H. pertussis* and may be different from, and not always run parallel with, protective potency. In any event it would scarcely be practicable to estimate the agglutinin response in children before each batch of vaccine produced commercially was issued for general use.

Of the three laboratory tests, therefore, the mouse intracerebral challenge test is considered, on the basis of present evidence, as the most satisfactory. It is correlated with protection in children, and in mice it measures protection from infection with a virulent strain of *H. pertussis*. A British standard pertussis vaccine has been established in terms of which the potency of other vaccines may be assayed by means of comparative tests. The standard has been prepared from vaccine V12 (Table I), which gave substantial protection in the field, by freeze-drying in 6% dextran. No instability has been detected in the dried standard, and its use in comparative tests will be the subject of a separate communication (Armitage and Perry, 1956).

In view of these results it would seem wise before the issue of a vaccine for use in children to submit it to the mouse intracerebral protection test to ensure that it has an adequate potency in relation to the British standard vaccine. It is also clear that a vaccine need not necessarily be made by the Michigan method; the results of the present trials show that one produced from cultures made in a liquid medium can give equally good results.

SUMMARY

In two series of field trials, 14 pertussis vaccines were tested for their protective potency in 28,799 children. The vaccines used in the first series of trials were poor, but those in the second series gave substantial protection, which was maintained for at least two and half to three years after vaccination.

At the same time as the field trials were in progress, laboratory tests were made in which the vaccines were tested for their ability to protect mice against intracerebral pertussis infection. Some of the vaccines were also tested for their ability to produce specific agglutinin in mice and in children.

A comparison between the field and laboratory results showed some correlation between the potency of vaccines in protecting children and their ability to protect mice against intracerebral infection. There was also evidence of a correlation between protection in children and ability to produce agglutinin in both mice and children.

It is concluded that in future only those pertussis vaccines which have been shown, by the intracerebral mouse-protection test, to have an adequate potency in relation to the British standard pertussis vaccine should be issued for use in children.

The Whooping-cough Immunization Committee of the Medical Research Council and the medical officers of health in the areas where the trials were made are grateful to the parents who consented to have their children injected. They wish to thank Glaxo Research Laboratories, the Lister Institute of Preventive Medicine, the Michigan Department of Health, the State of New York Department of Health, and the Wellcome Research Laboratories for the free supply of the pertussis vaccines, and the World Health Organization for its interest and for some financial help towards the cost of the second series of trials. They particularly wish to record their indebtedness to Dr. Pearl Kendrick, corresponding member of the Committee, who gave help and advice on the preparation of the vaccines during visits to this country and also by correspondence. The vaccine for the preparation of the British standard pertussis vaccine was generously provided by Glaxo Laboratories.

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Medical Memorandum

Repeated Delayed Splenic Bleeding Into the Lesser Sac

Spontaneous rupture of a normal spleen is a rare occurrence, and only about 100 cases have been reported in the world's literature. The case described below appears to be the first recorded instance where haemorrhage took place almost entirely into the lesser sac of the peritoneum, and is the first example of spontaneous splenic rupture in a case of arterial hypertension.

CASE REPORT

A woman aged 29 was admitted to hospital on April 14, 1951. Two days previously she had been discharged from another hospital, having had an operation there about six weeks before "for bleeding from a mesenteric vessel." On the day of admission she took a laxative for constipation, after which generalized abdominal pain and vomiting began and continued up to the time she was examined (3 p.m.). On direct questioning she admitted that about 24 hours

previously she had had left shoulder-tip pain which had continued for several hours, but it had disappeared at the time of examination. She felt very weak. She said she had some "heart trouble," but that her symptoms of that complaint, chiefly headaches, had been much less noticeable during the past few weeks. Her last menstrual period was in February, 1951. No other symptoms were present. Her doctor sent her to hospital with a diagnosis of ? ruptured ectopic gestation, ? internal haemorrhage.

Two previous pregnancies were normal. She had had occasional bouts of epistaxis, heavy menstrual periods, and excessive bleeding following dental extractions. The previous hospital admission had been advised because of symptoms similar to those presenting now. In addition, whilst an in-patient there, about two weeks previously, she experienced a bout of abdominal pain and vomiting lasting a day or so, which was diagnosed as "gastritis." Her mother had died at 36 years of age from "a stroke."

The patient was a thin, pale woman, anaemic and shocked. The pulse rate was 130 a minute, temperature 97° F. (36.1° C.), respiratory rate 20, blood pressure 90/? mm. Hg. Examination revealed no gross cardiac enlargement; an apical systolic murmur was present. The lungs were normal. In the abdomen, distension was obvious. A healed scar extended from the pubis to half-way between the xiphoid and umbilicus. There was no rigidity, but generalized tenderness was found. Peristalsis was absent. Vaginal examination revealed no abnormality. Later, under general anaesthesia, a mass was palpable in the epigastrium. It was dull, and the dullness was continuous with liver dullness. A provisional diagnosis of intraperitoneal haemorrhage ? due to leaking splenic aneurysm was made.

After resuscitation, operation was undertaken on April 15. Through a midline epigastric incision the mass previously felt was seen to be the stomach pushed forward by a lesser sac full of old blood clot. There was unclotted blood in the greater sac. The spleen was adherent to the diaphragm and not easily mobilized, and it was removed; the splenic vessels had previously been ligated in continuity proximally, lest the site of section be placed distal to a ruptured aneurysm of the splenic artery. The abdomen was closed in layers and a stab drain inserted.

With the spleen were two splenuli and the tail of the pancreas. The weight of the total specimen was 450 g. Most of the upper half of the organ was occupied by old blood clot, which had disorganized the pulp. There was a tear in the capsule on the diaphragmatic surface of the spleen, but no large subcapsular haematoma otherwise. The haematoma surrounded the pedicle. No aneurysm was found. The splenic vein was thrombosed.

Convalescence was protracted owing to the development of a *Staphylococcus aureus* coagulase-positive bacteraemia, which was finally controlled with chlortetracycline. On discharge her blood pressure was 195/140 mm. Hg.

On August 11 she was readmitted because of intractable vomiting. She stated that polyuria and polydipsia had appeared since the operation. She died on September 17.

Post-mortem examination (Dr. E. Milford Ward): Tuberculous meningitis, without evidence of tuberculosis elsewhere, was found. Heart: marked hypertrophy of the left ventricle. Both kidneys were reduced in size. The capsules stripped with difficulty and the surfaces were coarsely scarred. Histologically they showed the picture of chronic non-suppurative pyelonephritis.

COMMENT

This was an interesting clinical problem of diagnosis. Common causes of severe anaemia (Hb 29%) in a female are nutritional, or due to bleeding from the genito-urinary or gastro-intestinal tracts. Other possibilities considered here were splenic infarction from subacute bacterial endocarditis, and polyarteritis nodosa acuta. But no other signs

of endocarditis were present, and muscle biopsy done at laparotomy was negative.

The presence of essential hypertension favoured the possibility of an arterial source of bleeding, such as a leaking aneurysm. Chevallier and Bernard (1944) have shown that vascular arterial lesions are the second commonest cause of haemoperitoneum in women, although occurring 25% less often than in men. It is rare to make a correct pre-operative diagnosis. Of 41 cases previously reported, only 2 were accurately diagnosed.

The occurrence of this case completes the possible anatomic-pathological picture of haemorrhage from the spleen. Recalling the fact that this organ lies in relation to two peritoneal lined cavities, and that a postero-lateral relationship to the kidney brings it into contact with an extra-peritoneal area, there are three possible ways in which symptoms and signs may present: (1) the commonest is bleeding into the greater sac, diagnosis often being confused with other causes of peritoneal irritation; (2) the next most frequent one is rupture into the lesser and greater sacs, a pancreatic lesion being most often diagnosed; and (3) the rarest is extraperitoneal extension into the loin, where a renal lesion is usually suspected. The present case is the first in which major and repeated bleeding took place into the lesser sac.

In several cases of normal spleens undergoing rupture a predisposing cause has been found. Undue mobility due to absence of the phrenico-colic ligament is said to occur in 2% of subjects (Susman, 1927). A vascular abnormality confined to the spleen—namely, angioma—has been once reported (Mondor and Boutron, 1938), but such a spleen is not truly "normal." Various alterations in contour with partial deficiency have also been found, but rupture did not always take place at the site of abnormality. It was impossible to discover a predisposing cause in this case.

The commonest event initiating spontaneous rupture is sudden increase in blood volume in the splenic vein. In the absence of any pertinent history this could not be established here. According to Price (1950) aseptic infarction of the spleen is commoner than realized and is often found in cardiac disease. In the absence of other evidence it must be assumed that this was the primary event in the present subject: an infarct was certainly shown microscopically.

Splenic histology is notoriously difficult to interpret. Wohl (1925) noted that, by the age of 36, 50% of spleens showed evidence of intimal thickening and hyaline change in the Malpighian bodies. Evidence of hypertensive disease is difficult to find unequivocally in this organ and was not found here, although other arteries in the body showed a characteristic histological picture of arterial hypertension.

It could not be established what the initial event producing haemorrhage was, and the relation of coexisting arterial hypertension remains speculative if not entirely coincidental.

I wish to thank Mr. J. C. Barrett for permission to publish this case and also Dr. E. Milford Ward, who reported on the specimens and performed the necropsy.

J. G. CALLANAN, F.R.C.S.,
London Chest Hospital, Arlesey, Beds.

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To help local authorities in their Clean Food campaigns the Ministry of Health has produced a new coloured poster on the theme "Hands Spread Germs." A series of pictures and slogans emphasizes the importance of covering cuts and sores, fingering food as little as possible, and washing hands thoroughly before preparing food.