The reasons for such an operation are quite different in an acute and in a subacute stage. In an acute stage, when the capsule is incised the kidney bulges out, and therefore it might be claimed that relief from tension is afforded. In practice, however, the operation seems to have been generally abandoned, and inasmuch as most cases pursue a favourable course on ordinary lines such a serious procedure is never justified. In the subacute cases the capsule has adapted itself to the increased size of the kidney, and operation can only be justified on the plea of establishing collateral circulation, and thereby arresting a progressively downward course. Most physicians who realize that recovery from an operation does not always mean cure of a disease, and who realize the many variations in course taken by subacute nephritis, will hesitate long before recommending surgical intervention. In a recent paper, however, Fawcett urges the value of the operation in a specially selected group of subacute parenchymatous cases, the sequelae, for the most part, of acute inflammation.

When uraemic coma develops, either subsequent to or independent of epileptiform convulsions, and when all ordinary measures such as hot packs, the use of pilocarpine in small doses, and purging fail to produce rapid improvement, venesection should be performed. I well remember the first case upon which I performed venesection, some twenty-five years ago.

A boy, aged 18, was admitted suffering from acute nephritis. After a few days he was well on his way to recovery. At this stage his friends managed to bring in a large supply of food, and the boy enjoyed a surreptitious but hearty meal. That evening he had a severe convulsion and passed into a state of coma. During the next day the coma persisted and there was almost complete anuria. The next morning, thirty-six hours after the beginning of the coma, he was still deeply unconscious, and apparently going downhill. I bled him to the extent of about 15 oz.; a few hours afterwards he opened his eyes, and that evening he again became conscious, and ultimately made a good recovery.

When bleeding a serious case, if the blood flows badly, it is worth remembering Lauder Brunton's tip that inhalation of oxygen will make the blood less treacherous and greatly facilitate procedure. It is curious that some writers, such as Tweedy, regard bleeding as dangerous in eclampsia, but most gynaecologists are in favour of moderate venesection.

During the war I practised lumbar puncture in addition to venesection for the repeated convulsions that were so frequently encountered. The most recent writers seem to regard lumbar puncture as a mistake, but I am convinced that no harm ever resulted in my own cases, and, judged as a clinical procedure, it appeared to have a beneficial result. It seems, indeed, to be a common-sense method of treatment. The cerebro-spinal fluid, as already stated, is under high pressure, and contains an excessive amount of urea and of chlorides. Removal of fluid is often good for the headache of chronic renal disease, and I therefore find it hard to believe that relief of tension will not be beneficial in acute renal disease accompanied by nervous phenomena.

The giving of saline injections intravenously, subcutaneously, or into the colon in uraemia is of doubtful value. For a couple of years I employed Fischer's solution both intravenously and by the rectum, but could never satisfy myself that it was of value, and the rectal injection of the highly alkaline solution which he recommends, containing as it does 10 grams of sodium carbonate per litre, is extremely irritating. The injection of plain sodium chloride and of sodium citrate solution can be justified only as a diluent of retained toxins, and may be useful in this way, even though it is realized that the kidney finds difficulty in excreting both chloride and sodium ion. On the whole, I am inclined to recommend their use in the form of colonic injections after thorough evacuation of the colon.

As regards drugs, morphine, so long under suspicion in uraemic cases, is now recognized as both safe and satisfactory in checking repeated convulsions. It is hard to realize why this remedy was so long under suspicion, having regard to the fact that in the allied condition of eclampsia it has been employed for many years.

ACUTE NECROSIS OF THE PANCREAS.*

BY

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THE term "pancreatitis" as the subject of this discussion was deliberately chosen so that it might cover the wide range of conditions usually included under that heading, many of which are but little understood: in order that those taking part in the discussion should not be tied down to any particular type, but might be able to give their views and experience of the many varieties of the condition, and especially of the less regular types or "formes frustes" of this somewhat rare disease.

In the few remarks that I have to offer, largely based on six cases of which I have had personal experience in the last two years, I propose to limit myself to the condition known as acute necrosis of the pancreas, which is a better term than acute haemorrhagic pancreatitis, as it does not beg the question of its primarily inflammatory origin, a view which is not held by a very considerable number of observers. Nor is the term "haemorrhagic" entirely satisfactory, as in a certain proportion of cases haemorrhage is not always strikingly in evidence.

THE PECULIAR FEATURES OF DISEASE OF THE PANCREAS.

The pancreas has been well described as a laboratory of chemical physiology. In addition to its internal secretion, it forms the most powerful proteolytic ferment, the fat-splitting and the amylolytic, in addition to others of less importance. Another feature of this gland in which it differs from other secreting glands is that it possesses two ducts, sometimes in anastomosis, sometimes not, and of which, to use an Irishism, the lesser—the accessory duct of Santorini—is sometimes the greater. The latter duct has no valve at its entry into the duodenum, a fact the importance of which will be seen later. The main duct of Wirsung in the majority of cases joins the bile duct before it pours its contents into the duodenum, the distance of this junction from the intestinal opening varying from zero to 11 mm., averaging about 4 mm. All these facts have a bearing on the canalicular theory of pancreatic necrosis.

In the view of many writers on the subject the varying forms of acute pancreatitis as described in the textbooks are simply stages of the same process, and are described by Brocq¹ as acute oedematous pancreatitis, acute haemorrhagic pancreatitis, and gangrenous and suppurative pancreatitis, the rarity of the first being due to the fact that the surgeon seldom sees cases at this early stage.

As regards the suppurative varieties, probably some are primarily infective, whether the infection is duct-borne or by way of the lymphatics, but many are simply secondary infections following on the necrosis of the gland.

In studying the various papers and case reports of acute pancreatitis one cannot but be struck by the varying types of the disease which they describe, the great difference in the mortality of different clinics, the diverse views held as to its etiology, and in some degree also as to the appropriate treatment.

This is perhaps not to be greatly wondered at, when, in a condition relatively uncommon, it can only fall to the lot of any individual surgeon to meet with a limited number of cases. Further, in many of the necropsy reports there is no account of a minute examination of the ducts which would throw some light on the etiology. In reading the papers of Deaver and other supporters of the theory of lymphatic extension from the gall-bladder it would appear that, as is well put in a paper by Fiske Jones,² they are describing a condition different altogether from that of acute pancreatic necrosis, and that whilst that theory may well account for chronic pancreatitis and some of the suppurative varieties, it is not applicable, at any rate, to the majority of cases of the former condition.

ETIOLOGY.

The immediate cause of the production of the *drame pancreatique* is the setting free of the secretion of the

* Read in opening a discussion in the Section of Surgery of the Annual Meeting of the British Medical Association, Cardiff, 1928.

pancreas and its activation in the ducts of the gland. In order that this may take place it is necessary first that the gland should be in the phase of secretion; secondly, that the proferments should be activated by some agent or other. When these conditions are fulfilled we have all the factors required for the production of pancreatic necrosis. On the extent to which this takes place and the duration of the process depends the varying severity of the different types of the disease.

The importance of the first condition is shown by the experiments of Brocq, in which bile was injected up the duct of Wirsung, it being found that haemorrhagic necrosis resulted only in those cases in which the dog had received a full meal some hours previously. Clinically it is often noticed that the sudden onset of the disease occurs after a heavy meal.

The second condition, activation of the proferments, may be fulfilled in one of several ways. Brocq found that normal bile would do this if the first condition was fulfilled. Archibald found that bile deprived of its mucus, or in which the salts were concentrated, was efficient. Succus entericus, the normal activant, as might naturally be expected, would also activate the secretion, and might gain access to the gland through a patent duct of Santorini. In addition to these the products of the cytotoxicity of gland cells and leucocytes, calcium salts, and bacteria may have the same result. For those who hold the theory of Deaver of a lymphatic extension of inflammation from the gall-bladder and a primary inflammatory pancreatitis, these would furnish the activating agent, and may give an explanation of some of those cases which are unassociated with disease of the biliary tract.

It is therefore probable that acute necrosis may be produced in more than one way. At the present time there are three main theories of its causation.

1. That it is due to a vascular lesion—embolism of pancreatic arteries or thrombosis of pancreatic veins.

This theory, defended by Gilbert, Chabrol, and Lépine, has probably few adherents, and little can be advanced in its support. That in certain cases thrombosis of pancreatic veins may be found *post mortem* is what might well be expected with a sloughing or suppurating mass of tissue. As regards an arterial origin, with the rich vascular supply and anastomosis of the pancreatic arteries, this does not appear a very likely cause (Brocq¹). Experiments on dogs in which arteries have been blocked by inert powders injected into the arteries have failed to produce the lesions of pancreatic necrosis.

2. The infective theory, strongly upheld by Deaver and Mangeret, and lately supported by Graham, Judd, and Mann, of infection spreading by way of the lymphatics from the gall-bladder to the head of the pancreas, to what Deaver terms the triangle of infection.

Against this theory it may be said that in the vast majority of instances the haemorrhagic fluid in the general abdominal cavity and in the lesser sac is sterile. Kauffmann,² in a series of experiments on cats, in whom he infected the liver with staphylococci and traced the infection to the gall-bladder and through the lymphatics of the common duct to the pancreatic lymph gland, found no lesions in the pancreas resembling acute necrosis.

As infections of the gall-bladder, accompanied or not by calculi, are common enough, it is difficult to see why this spread of infection and its resulting acute pancreatitis does not occur more frequently. Again, it is by no means uncommon to find posterior ulcers of the stomach perforating on to the pancreas, which in some cases actually forms the floor of the ulcer; but in a series of 340 cases of acute pancreatitis collected by Brocq, in only 2 was a gastric ulcer, and in 3 a duodenal ulcer, mentioned as a possible cause of the condition, and yet one would imagine that this would furnish a ready means of conveying infection to the pancreas.

3. The theory that necrosis is caused by regurgitation of bile up the pancreatic ducts.

Since the classical work of Opie³ this view has been held by many, and the investigations of Brocq and Binet and of Archibald⁴ have greatly strengthened it. The pancreas is protected from self-digestion by several safeguards. The proteolytic ferment is inactive in the gland

in the state of protrypsin, and remains so normally until it encounters the enterokinase of the succus entericus in the duodenum. Of the condition of the lipase less is known, but it is known that if bile is not necessary to activate the lipolytic ferment it very greatly increases its action in splitting fats.

In experiments by Brocq and Binet it was found that when the duct of Wirsung in the dog was divided and left open in the peritoneal cavity fat necrosis did not ensue, but if at the same time the gall-bladder was opened and the bile and pancreatic secretion were allowed to mix, haemorrhage and steato-necrosis followed. Further, whilst the injection of normal bile into the ducts of a fasting dog had no apparent effects on the gland, when injected after a full meal the typical appearances of acute haemorrhagic necrosis followed in due course. It was further found that the active agent was the glycocholate of soda, whilst the taurocholate and the pigment gave a negative result.

As regards the mechanism by which bile may gain access to the gland, there is that first described by Opie, where a small calculus was found impacted at the bile papilla, the bile duct and the duct of Wirsung thus being thrown into a common channel. A considerable number of such cases have been reported, and many more have probably escaped observation, the stone having either passed on during the course of the illness or having been dislodged in the manipulations of the necropsy. Incidentally it is worth noting that in quite a number of reports it is stated that the stones in the gall-bladder were very small, this being so in 4 out of 6 of my own cases, where the stones were of such a size that they would be competent to block the opening at the bile papilla without at the same time blocking the duct of Wirsung. This can only occur in cases where the length of the ampulla is at least twice the diameter of its opening into the duodenum. Such a condition, it is said by Judd and Mann,⁵ can only occur in 9 of 200 individuals, but Opie found in 100 cases at necropsy that it could take place in 30 out of 100. Even taking the former view as correct, in a comparatively rare disease 9 in 200 possible persons would not be an argument against this method of production. Spasm of the sphincter of Oddi has also been invoked as a means by which the two channels can be thrown into one. Against this it has been said that this sphincter also encircles the duct of Wirsung, and so would tend to close it. As regards the low pressure of bile in the ducts, Judd and Mann⁷ found that vomiting would raise the intraductal pressure to 1,000 mm. of bile.

There are other ways by which the secretion in the ducts of the pancreas can be activated, and the normal activant is the succus entericus. In 10 of 100 individuals Opie found the duct of Santorini larger than, or equal in size to, the duct of Wirsung. The opening of this duct has no valve; violent vomiting would therefore be competent to force duodenal contents into the substance of the pancreas.

Archibald, in his experiments on cats, in which animals the duct of Wirsung joins the common duct as in man, used (1) infected bile, (2) human bile sterilized and deprived of its mucus, (3) solutions of bile salts. Spasm of the sphincter of Oddi was produced by the application of hydrochloric acid to the bile papilla after opening the duodenum, and the fluid was injected into the gall-bladder at graduated pressures. Infected bile, in one instance, caused death in an hour, but whether this was due to a definite pancreatic lesion is doubtful. With the second two substances, where the animals died or were killed at varying periods, he found cytolytic necrosis of masses of secreting cells. In those animals which survived and were later killed it appeared that the necrotic foci were in process of absorption and repair by formation of fibrous tissue. He points out that it is probable that bile may enter the pancreatic ducts in some cases without doing harm, in others that focal necrosis may occur as the result of cytotoxicity but without activation of the ferments and autolysis, and that many cases probably occur of mild attacks of pancreatitis which are undiagnosed and go on to the condition of chronic pancreatitis.

The conclusions he draws from these experiments are that infected bile enters the pancreatic duct owing to spasm of the sphincter of Oddi, such spasm resulting from

passage of gall-stones, a duodenal ulcer, etc., with or without increase of pressure in the biliary system, caused by vomiting.

As an inference from this he considers that the correct treatment of the condition is to decompress this system, and suggests that this may be effected by transduodenal exposure and division of the sphincter of Oddi, pointing out that cases of impacted stone in the ampulla in which this operation is performed usually do well. It is doubtful if a patient suffering from acute pancreatitis would stand such a heroic and time-consuming procedure, and if the immediate result would be more readily obtained by cholecystostomy or choledochus drainage. If, later, division of the sphincter seemed desirable, it conceivably might be done from within by an instrument on the lines of a urethrotome.

As regards his view that the retrojection of bile is due to spasm of the sphincter, it appears highly probable that this is the cause in a certain proportion of cases. The sphincter may embrace the common duct distal to the junction of the duct of Wirsung, in which case spasm would throw the ducts into a common channel. In others, fibres of the sphincter also surround the duct of Wirsung, and spasm would close both ducts and prevent the retrojection of bile (Judd⁶). Judd states that the former arrangement only holds in 4.5 per cent. of bodies examined, but as Moynihan⁸ says, "Is it not possible, indeed probable, that they are present in a large proportion of those patients who suffer from acute pancreatitis?"

The tone of the sphincter is 100 mm. of water, but when thrown into spasm can resist probably 600 mm. (Judd¹¹). The maximum secretory pressure of the bile is 300 mm., but vomiting will raise the pressure in the ducts to 1,000 mm. It is known that after removal of the gall-bladder the extrahepatic ducts first dilate, and that only subsequently does the sphincter become incompetent. Is it not possible that some cases of acute pancreatitis which have followed on a cholecystectomy are due to the resulting spasm of the sphincter of Oddi and the rise of pressure in the common duct, especially in cases where there has been previous damage to the pancreas?

Among the rare causes of pancreatitis, one of some interest, and of which 50 instances have been collected from the literature, is that of the entry of an ascaris into the common duct and thence into the duct of Wirsung. The ascaris itself is not digested because it contains an antitrypsine, but it carries into the duct some of the duodenal contents. The factors of trauma and activation are here both present. An interesting picture of the worm lying in the duct of Wirsung, and the resulting pancreatic necrosis, is shown in a paper by Schmieden and Sebening.⁹ In this same paper, based on a series of 2,137 cases of pancreatitis during the past eight years, obtained by a questionnaire addressed to 100 clinics, a list is given of 145 cases which followed on various abdominal operations. These cases consisted of acute pancreatitis, purulent pancreatitis, abscess, and fistula.

As the operative procedures that they followed are very suggestive and of importance to the surgeon, I may briefly mention some of those given by these authors. Especially to be noted is burying the duodenal stump in the pancreas, or damage to the duct of Santorini by sutures in the same procedure after gastrectomy, or in mobilizing the duodenum or resecting a duodenal ulcer, including the tail of the pancreas in the ligature of the splenic vessels in splenectomy or of the kidney pedicle in nephrectomy, pushing up a calculus impacted in the ampulla, and the retrograde passage of a sound in transduodenal choledochotomy. They also state that although a piece of pancreas may be excised with impunity in 99 per cent. of cases, in the hundredth it may be followed by pancreatitis. It is interesting to note that they suggest that leakage at the suture line in gastrectomy after technically perfect suturing may be due to unrecognized injury to the pancreas and digestion of the catgut. In a case of gall-stones with cholangitis in which I washed out the duct with saline, although at operation there was no trace of pancreatitis the patient died two or three days later, and at necropsy a purulent pancreatitis was found.

That pancreatitis may arise from a chemical substance in the blood stream is shown by a fatal case after cholecystography, although another explanation is that the bile containing the concentrated dye reached the pancreas by way of the ducts.¹⁰

DIAGNOSIS.

Regarding the pre-operative diagnosis, that this appears to have been correct in a restricted number of cases is due, in the words of Korte, to two reasons: first, that one does not always bear in mind that a sick person possesses a pancreas, although lesions of the gland are more common than is generally supposed; secondly, its symptoms are easily confounded with other more common acute abdominal conditions, acute intestinal obstruction, and the various conditions of the gall-bladder which so often precede or accompany the attack of pancreatitis. But I think it is rather that the idea of pancreatitis is so associated with the fulminating variety, the symptoms of which are well known and where the failure to diagnose is less likely to occur. It is in the "formes frustes" of pancreatic necrosis that the real difficulty arises.

During the past two years I have had six cases of pancreatic necrosis under my observation. Two of these I may briefly refer to as illustrating this difficulty.

One, an unmarried woman, aged 32, was brought to hospital as an emergency case, and was sent home. She was admitted a week later on my receiving day. I then saw her, diagnosed gall-stones, and she was put on the list for my next operating day, as her condition appeared in no wise urgent. When the abdomen was opened a gangrenous gall-bladder was found with two families of gall-stones, one moderately large, one very small. There was extensive fat necrosis in the omentum and mesentery. The gall-bladder was removed and the abdomen drained. Three days later a large abscess formed and was opened up. At necropsy a week later the pancreas was found almost totally necrotic.

The following case illustrates the fact that the condition may be missed at operation.

A man, aged 55, who had had an attack of biliary colic a year previously, was suddenly seized with severe abdominal pain and became jaundiced. When the abdomen was opened the gall-bladder, full of stones, was found to be perforated, the perforation being sealed off by omentum. There was some blood in the upper abdomen which was thought to have come from a vessel in the omentum. There was no fat necrosis and the pancreas was not exposed. The gall-bladder was removed. A few days later the wound opened up and an abscess burst, the entire pancreas forming a black slough lying in the abscess cavity.

These and other cases have made me feel that the current teaching that acute conditions of the gall-bladder, empyema, etc., should be allowed to settle down and be operated on *à froid* is entirely wrong. In my opinion they are almost equally urgent with the acute appendix. Further, that where there is the slightest suspicion of the condition of the pancreas, it should be exposed to direct vision through the gastrocolic omentum.

Regarding laboratory methods of diagnosis, these are seldom available; the diastatic index, obtaining pancreatic secretion by the duodenal tube, and the estimation of blood sugar might be carried out in the less acute cases, while Loewi's test is readily performed, and if positive might help to confirm the diagnosis, although in one case it misled me.

A woman, aged 70, was admitted as a case of acute abdomen with an indefinite previous history. She had a sudden attack of generalized abdominal pain, moderate rigidity, and tenderness most marked in the epigastrium and left costo-vertebral angle. Adrenaline in the right conjunctiva gave a most marked dilatation of the pupil. The abdomen was full of sero-purulent fluid, which was found at the necropsy to be due to peritonitis following on carcinoma of the bladder.

TREATMENT.

In respect to treatment, the case records of various clinics differ. In some cases abdominal drainage of the region of the pancreas only, in others incision of the gland, gauze tamponade, and drainage, have given good results. In others, drainage of the biliary tract through the gall-bladder or common duct is added, and it is difficult to see which has given the best results.

It appears certain that under no conditions should the gall-bladder be removed, and I should say that even a gangrenous gall-bladder should be simply drained.

Two drugs, aspirin and hexamine, are secreted by the pancreas, and their administration theoretically might be

supposed to have some action in disinfecting the gland, and could at least do no harm.

Ohno and Schonback have immunized animals to trypsin, and have suggested immunization by an antitryptic serum, but I do not know if this has ever been carried out on human beings. The administration of atropine might be worth a trial on account of its inhibiting action on pancreatic secretion.

It is not impossible that some of the milder cases of this condition recover without operation, since pancreatic cysts may take their origin in a limited necrosis of the gland and escape of small quantities of secretion.

The indications as regards operative treatment are, in my opinion, to expose the pancreas through the gastrocolic omentum, to incise the peritoneum over it, and to place rubber drains to the swollen area and gauze tampons around to wall off the peritoneum and prevent the diffusion of the escaping secretion. It appears that more harm than good may be done by incising the pancreas itself, which might divide ducts and set free more ferments. If the gall-bladder was distended I should do a cholecystotomy, and if the common bile duct appeared distended I would drain this. Neither of these procedures should take much time or involve much disturbance of the parts or increase the shock. The result would then depend on the extent of the original damage to the pancreas.

REFERENCES.

- ¹ *Les Pancréatites Aiguës Chirurgicales*. By Pierre Brocq. Masson et Cie, Paris, 1926.
- ² Fiske Jones: *Surgical Clinics of North America*, August, 1922, vol. 2, No. 4, p. 1130.
- ³ Mark Kauffmann: A Study of the Lymphatic Theory of Pancreatitis. *Surg., Gynecol. and Obstet.*, vol. xlii, January-June, 1927, p. 15.
- ⁴ Eugene Opie: *Disease of the Pancreas*. Lippincott Company, Philadelphia, 1910.
- ⁵ Edward Archibald: An Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter. *Surg., Gynecol. and Obstet.*, vol. xxviii, June, 1919, p. 530.
- ⁶ E. S. Judd: *Journ. Amer. Med. Assoc.*, 1921, vol. lxxvii, p. 197.
- ⁷ Mann: *Mayo Clinic Papers*, 1921, vol. xiii, p. 185.
- ⁸ Sir Berkeley Moynihan: *Annals of Surgery*, vol. 81, 1925, p. 139.
- ⁹ Schmieden and Sebening: Surgery of the Pancreas. *Surg., Gynecol. and Obstet.*, June, 1928, vol. xlii, No. 6, p. 735.
- ¹⁰ Bruce, M. Dick, and Victor G. H. Wallace: Cholecystography—a Clinical and Experimental Study of the Toxic Effects of the Dyes. *Brit. Journ. of Surg.*, January, 1928, vol. xv, No. 59, p. 361.
- ¹¹ E. S. Judd: The Recurrence of Symptoms following Operations on the Biliary Tract. *Annals of Surgery*, Part 304, April, 1918, p. 473.

THE CONTROL OF SMALL-POX.*

BY

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THE manifestations of small-pox in recent years have been characterized by (1) a very marked decrease in incidence, and (2) an almost universal decrease of the case mortality rate.

The case mortality rate has decreased partly through (a) the spread of alastrim, or a very mild type of small-pox, which seems quite unaffected by the trend of the ordinary small-pox, and partly through (b) a more favourable course of ordinary small-pox cases in many countries. It must be added that important outbreaks of severe small-pox have not ceased to occur, a fact of which we are reminded by the Rio de Janeiro outbreak in 1926, and that of Algeria in 1926-27.

In regard to the decrease of incidence in Europe it should be emphasized that this is not the first time it has fallen to a very low level, and also that the decrease is not universal. Though there were only 652 small-pox cases in Europe in 1927, outside the United Kingdom, the Iberian Peninsula, and Russia, 280,000 cases were notified that year in the whole world. If we add China and parts of Africa and South America, where cases are not reported, the total number of cases must certainly have largely exceeded 300,000. In India alone small-pox causes 50,000 deaths in an average year.

It must be borne in mind that small-pox is of a more truly epidemic character, in its year-to-year movements, than most other diseases. It attains a high incidence for some years, and falls then to a very low level. It is only

in India that small-pox appears to be endemic at a constant level, but the size of the country accounts for this seemingly paradoxical phenomenon.

Even in the twentieth century very marked fluctuations in the incidence have been noted. A first epidemic wave occurred during the years 1901 to 1903. In England, London and the neighbouring counties were chiefly affected in 1901 and 1902; Lancashire and the northern counties, in which the mild small-pox was later to become prevalent, were affected during the following two years. Small-pox caused more than 4,000 deaths in England in these four years, when the classical type of the disease prevailed.

In other European countries it was no better; in Belgium there were 2,938 deaths from small-pox during the three years 1902 to 1904, with a maximum in 1903; in French towns of over 5,000 inhabitants, 4,903 deaths from small-pox were reported in 1902 and 1903. In Italy small-pox was epidemic from 1901 to 1904, during which years it accounted for 14,951 deaths.

Further east in Europe the wave had come a few years earlier; in Austria and Hungary its maximum occurred between 1897 and 1899, in Rumania in 1896 and 1897, and in Russia in 1898 and 1899.

Although a high endemic level persisted in Russia, Spain, Italy, and, probably, in the Balkans, with the exception of Rumania (maximum in 1906, 1909, and 1913), there were no further serious outbreaks in England and in northern and central Europe until 1920. In Italy there were new outbreaks in 1911 and 1912, 8,164 deaths having been attributed to small-pox.

Small-pox of severe type was widespread from 1901 to 1903 also in the United States; 3,578 deaths were reported during those three years in the registration area, which then only included about one-third of the country. The incidence fell subsequently, and from 1906 to 1909 it was as low as, or lower than, it had ever been.

Small-pox was widely prevalent in Japan in 1892, 1893, and in 1897—the same years as there were extensive epidemics in eastern Europe. During the first-mentioned two years 22,261 deaths were ascribed to small-pox, and in 1897, 12,276. Its incidence subsequently fell, and in each of the years between 1900 and 1903 only from four to seven deaths from small-pox were reported, indicating a much more favourable situation than in any of the years subsequent to 1915. There was a new epidemic in 1908, which caused 5,838 deaths. The incidence of small-pox increased again in 1917, and, although it has decreased considerably in recent years, there were still 92 deaths from small-pox in 1927.

We have to wait for the years of the war to witness a renewed increase of small-pox in southern, eastern, and central Europe. In the United Kingdom, the Netherlands, France, and northern Europe there was no increase; in Germany it was moderate, 448 deaths being ascribed to small-pox in 1917, and 704 in 1919. In Austria (pre-war territory) there were, on the other hand, about 50,000 cases in 1915 and 1916.

In Italy the incidence was low during the war, and reached a minimum with only 16 deaths in 1916; but in 1919 and 1920 there were severe epidemics causing 27,417 deaths. It is interesting to note that this epidemic occurred almost exclusively in southern Italy, which was the case also with the outbreak of 1901 to 1904. The provinces particularly visited on both occasions were Apulia with Basilicata, Campania, and Sicily.

The crest of this wave of small-pox, which affected mostly eastern, southern, and central Europe, was in most countries reached in 1919. The incidence was still very high in 1920, but after that there was a general decrease, which has continued ever since. In certain countries the fall has been quite exceptional. Thus, in Rumania, where there were 20,523 cases in 1919, only 2 cases were reported in 1927. In Italy there were 34,363 cases in 1919, and only 59 in 1927. The number of cases reported in the Ukraine decreased from 34,730 in 1920 to 189 in 1927.

In 1927 fifteen European countries were altogether free from small-pox, while seven reported less than five cases each; in only eight countries were more than five cases reported. Exceptions to this general decrease have been extremely few. Besides England and Wales, where a mild form of small-pox began to spread in 1922, and Switzerland, where a similar mild type of small-pox was prevalent from

*The opening paper in a discussion in the Section of Preventive Medicine of the Annual Meeting of the British Medical Association, Cardiff, 1928.