chemotherapy in this respect. In a study of recurrences in pneumonia Strauss and Finland (1942) have shown that in those cases treated with sulphamamide there was a greater tendency for attacks to recur at shorter intervals, and for the same type of pneumococcus to occur more frequently in both attacks, than in those treated with serum or non-specific therapy. On the other hand, Jordan et al. (1950) have shown that, in any event, by the time the patient has symptoms the immune response has already been stimulated, and indeed that this response (measured by agglutination titres) was no different in those treated and those not treated.

The present work in mice suggests that there is some difference in the degree of immunity developed, depending on the method of treatment when using the same drugs. Under the conditions of these experiments, the subsequent immunity was greater following stoss therapy than that following the repeated treatment.

Now that chemotherapy is so effective in the treatment of numerous infections, we should, I suggest, take into consideration the more remote and long-term factors as well as the immediate effect of treatment. In this way prevention as well as cure may be achieved.

Summary

As a result of the good response observed in children with acute respiratory infection when treated with a single dose of penicillin and sulphadimidine (stoss-therapy), an experimental investigation into the relationship between method of treatment and subsequent immunity was planned.

The experiments were designed to investigate the immunity of mice which had been infected with virulent pneumococcus and then treated with a mixture of sodium sulphadimidine and penicillin. There were two different treatment groups: (1) a single massive dose of sulphadimidine and penicillin (stoss-therapy), and (2) six smaller doses repeated at intervals of eight hours. Treatment of both groups was delayed 10 hours after infection. Ten days later the survivors in each group were reinfected with challenging doses of pneumococcus, and the immunity of each treatment group was evaluated by mortality.

In each experiment except one the single-dose group (stoss) showed either a lower or a similar mortality on reinfection compared with the group having repeated doses. When all the results were taken together, a significant difference at the 1% level in favour of stoss-therapy was observed.

So far as these results can be applied to natural human infection, the greater immunity of the stoss-treated group over the repeated-dosage group offers a further reason for using stoss-therapy in suitable cases of human pneumococcal infection.

I thank Miss M. Mann for technical help and for her care of the animals; Dr. C. Mackenzie for help with the experiments; the pharmacological department for preparing the small doses of penicillin and sulphadimidine; and Dr. P. R. Evans, Professor R. Knoyle and Dr. P. E. Polani for their criticism of the manuscript.

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SPLENIC ARTERIAL ANEURYSM

BY

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Aneurysm of the splenic artery was mentioned by Beauassis in 1770. Winckler (1905) recognized the condition in the living, Högener (1920) made the diagnosis before operation, and Lindboe (1932) was the first to make a radiological diagnosis. Perhaps the most famous example was that of President Garfield, who died from a ruptured traumatic aneurysm of the splenic artery two months after being shot by an assassin.

Splenic arterial aneurysm is a rare condition, and rupture is usually fatal. Owens and Coffey (1953) reviewed 204 fully documented cases, and Hill and Inglis (1955) found 35 survivors after surgery, including only nine after rupture. A further four recoveries after rupture have been reported by Gallagher and Hudson (1954), Parrella (1955), Colangelo (1955), and Owen, Holmes, and Scannell (1957). Among these 13 survivors after rupture were four young women (Owen et al., 1957).

Diagnosis before rupture is uncommon (Huges and Joske, 1955; Riemeneschneider, 1955). Berger, Forsey, and Furst (1953) considered their case to be the eleventh diagnosed before operation in the English literature.

There are many unrecorded cases of splenic arterial aneurysm, particularly those seen at necropsy, and those diagnosed radiologically and not confirmed by operation.

The purpose of this paper is to discuss five patients with splenic arterial aneurysms operated on in Mansfield during the past two years. Four of the five survived. In two the aneurysm had ruptured; one, a pregnant women with a porta-caval shunt, recovered. The other three were diagnosed on radiological grounds before operation. In two the operative removal was incidental to that of a carcinoma—of the oesophagus in one, and of the kidney in the other. The remaining patient had urological symptoms and hypertension, but none referable to the region of the aneurysm.

Case 1. Staged Rupture—Splenectomy—Death in Anuria

A publican of 42 was admitted as an emergency case with pain in the left hypochondrium. A severe attack of pain in the left loin passing to the left chest in the mid-axillary line,
had occurred four days previously, but cleared up with rest in bed. He started work three hours before admission. There was a sudden very severe pain in the left hypochondrium; he became grey, sweating, and collapsed, but again improved.

He collapsed again soon after admission, and was thought to have had a coronary thrombosis or possibly an acute pancreatitis. He was pulseless and cyanosed, with epigastric and left-sided pain and tenderness. An electrocardiogram was normal, as were the urinary diastase and a plain radiograph of his abdomen taken as he began to improve. Next day his general condition was better and the pain was less, but it still occurred in spasms. The blood pressure was 130/80; the abdomen moved well on respiration, but there was general tenderness, with dullness in the flanks. His haemoglobin was only 52%. A diagnosis of intraperitoneal bleeding was made.

At operation (Mr. P. A. Read) the abdomen was full of blood and clots, with old clots in the lesser sac, into which the splenic aneurysm near the pedicle must have ruptured. Splenectomy was performed with excision of the aneurysm, and 2 litres of blood was transfused.

Although his immediate post-operative course was satisfactory, he became anuric, and died three days after operation.

Necropsy revealed extensive hypostatic pneumonia, parenchymatous degeneration of liver, kidney, and brain, and toxic petechiae on several surfaces.

**Case 2. Ruptured Splenic Aneurysm in Pregnancy after Porto-caval Shunt—Splenectomy—Recovery**

A housewife of 36 was admitted as an emergency case with gross intraperitoneal bleeding on December 24, 1956. She was known to have had an enlarged spleen since the age of 20, and Dr. R. J. Twort had confirmed that she had portal hypertension after a haematemesis in 1953. A splenic venogram showed an intrahepatic block. Liver-function tests were normal. In the summer of 1956 Mr. T. B. Field carried out an end-to-side porto-caval shunt. There was fine multilobular cirrhosis of the liver. The liver and spleen reached to the level of the umbilicus.

It then became apparent that she was in her third pregnancy. This was proceeding uneventfully, and she attended the antenatal clinic in early December. On Christmas Eve, in the 26th week of pregnancy, while doing the Christmas decorations, she had a sudden severe pain in the left side of the epigastrium passing to the right side, and she fainted. Dr. M. E. O'Sullivan diagnosed gross intraperitoneal haemorrhage from the spleen, and noted that her previously easily palpable spleen could only be felt on “dipping.” Mr. S. C. Anderson and the flying squad were summoned urgently, and 1 litre of blood was transfused without preliminaries. Fortunately, her blood group was known, and this prompt action enabled her to reach King's Mill Hospital alive.

At operation some four hours after her initial symptoms, some 3 litres of blood was sucked out of the peritoneum as well as clots. A bleeding aneurysm was found near the hilum of the spleen, and a splenectomy was performed with excision of the aneurysm. There had been considerable bleeding behind the peritoneum and into the mesentery. Her condition was critical during the operation, and a further 2 litres of blood was transfused by two drips. This operation was done under general anaesthesia, given by Dr. Mc Nab.

**Specimen.—**Dr. A. B. Hill reported that this showed a venous aneurysmal sac and two adjacent arterial aneurysmal sacs 4.4 by 4.2 and 2.2 by 3 cm. in the main trunk near the hilum. Both showed intimal degeneration, fragmentation, atherosclerosis, and patchy calcification. The larger sac showed an area of progressive thinning down to a focus of 0.7 cm.—a mural rupture. The specimen was radiographed, though it is unlikely that the degree of calcification would be recorded on a routine radiograph. The spleen showed reticular hyperplasia, and portal hypertension was suggested. There was no extraspleenic arteriovenous communication.

**Progress.—**The patient aborted on the second post-operative day. Later she had rigors and chest pains, and was considered to have had recurrent pulmonary infarcts associated with a *Streptococcus pyogenes* septicaemia. Dilatation and curettage was done for septic retained products by Mr. S. C. Anderson two weeks after operation. She was treated with penicillin and streptomycin, and later with erythromycin. She made a slow recovery, with a relapse of the septicaemia, again requiring erythromycin. She was well when seen fifteen months after operation.

**Case 3. Splenic Aneurysm and Left Renal Adenocarcinoma—Splenectomy and Nephrectomy—Recovery**

A housewife of 63 was referred with a history of left renal colic and haematuria for two weeks. There had been occasional pains in the left loin for three years. Physical examination was not informative. An intravenous urogram showed a filling defect in the left kidney and a calcified splenic aneurysm. Retrograde pyelography (Fig. 1) confirmed a space-occupying lesion in the kidney and also in the pelvis—possibly blood clot.

The kidney and spleen were excised through the bed of the eleventh rib, and recovery was uneventful. She was well when seen a year after operation.

**Specimen.—**The kidney showed a typical adenocarcinoma. There was a calcified aneurysm of the main splenic artery near its division measuring 3.3 by 1.5 cm. (Fig 2A).

**Case 4. Splenic Aneurysms and Carcinoma of the Oesophagus—Block Resection—Recovery**

A housewife of 75 was referred by Dr. J. C. Pease with dysphagia from a carcinoma of the lower oesophagus. She also had three calcified splenic aneurysms (Fig. 3). She had had a partial gastrectomy 20 years before by Mr. E. A. Nicoll for gastric ulcer.

Through the bed of the ninth rib a resection of the lower oesophagus, spleen, part of the pancreas, and remnant of the stomach was done, with a Roux loop oesophagojejunostomy. She was well when seen a year after operation.
Specimen.—The largest of the three calcified splenic aneurysms at the division of the splenic artery measured 2.9 by 1.8 cm. (Fig. 2C).

Case 5. Splenic Aneurysm and Pyelitis—Splenectomy—Recovery

A housewife of 57 was known to be hypertensive and overweight. She had had a partial thyroidectomy for toxic goitre four years previously. She now had what seemed to be a typical attack of pyelocystitis, due to Escherichia coli. There was some haematuria. An intravenous urogram showed normal upper urinary tracts and a calcified splenic aneurysm (Fig. 4). There was no other abnormality. The blood pressure was 190/110. The urinary symptoms responded to nitrofurantoin, to which drug the organisms were sensitive.

The spleen and the aneurysm were excised. Recovery was uneventful. She was well when seen a year after the operation.

Specimen.—The calcified aneurysm measured 2.6 by 2.1 cm., and was situated near the branching of the main trunk of the splenic artery (Fig. 2B).

Discussion

The features of this condition are well described elsewhere (Sherlock and Learmonth, 1942; Chalmers, 1949; Owens and Coffey, 1953; and others), and mention is here made only of the salient points.

Incidence

Owens and Coffey (1953) found 37 splenic aneurysms in 96,471 necropsies, an incidence of 38 in 100,000. It is the most common intra-abdominal aneurysm after that of the aorta. While other aneurysms are five times more common in men, splenic aneurysms occur twice as often in younger women as in men. The average age of identification is 48, and, in round figures, half the women are of child-bearing age, and half of these are pregnant.

All radiologists of experience have seen numbers of these calcified aneurysms, but I have not been able to find any large series or collected radiological statistics.

Pathology

The commonest pathogenetic factor is arteriosclerosis, then embolic phenomena, portal hypertension, congenital causes, trauma, and infection in that order of frequency.

Splenomegaly occurs in 45% of cases, and portal hypertension, as in Case 2, in half of these. Rupture in pregnancy occurs after the sixth month; in a third of these there is no obvious cause. In some patients rupture of the splenic artery occurs without a definite aneurysm. This was the case in three of the four previous recoveries after rupture in pregnancy, all these patients being women in their early twenties.

The aneurysm is single in some three-quarters of the patients, and in three-quarters the main trunk of the splenic artery is involved. The average diameter of the aneurysms is 3.1 cm.

Ruptures most commonly occur into the peritoneum, sometimes into the lesser sac or retroperitoneally, and occasionally into the stomach, colon, mesentery, and even into the chest.

FIG. 2.—Radiographs of the excised spleens showing calcified aneurysm. A=Case 3. B=Case 5. C=Case 4 (the specimen also includes some stomach, oesophagus, and pancreas).

FIG. 3.—Case 4. Plain radiograph showing three calcified splenic aneurysms.

FIG. 4.—Case 5. Plain radiograph showing calcified splenic aneurysm.
Clinical Manifestation and Diagnosis

The aneurysm may be an incidental finding, diagnosed by the characteristic roughly circular calcified shadow, often with a loss of continuity where the sac communicates with the artery, and with central stippling, as in Cases 3, 4, and 5. In these patients the position of the calcified aneurysm varied from opposite the eleventh dorsal to opposite the second lumbar vertebra. A host of symptoms, many referred to the gastro-intestinal tract, may be ascribed to the aneurysm, and unrelated urological symptoms may be present, as in Cases 4 and 5, and require radiography.

The usual symptom before rupture is pain in the abdomen, particularly in the left upper quadrant, sometimes radiating to the back, the chest, and the left shoulder. Between attacks the patient is often well. Some of these attacks of pain are probably small leaks, and there may be a "staged" rupture as in Case 1. Haemorrhage may be precipitated by trauma or exertion: the weekly wash, a fit of laughter, opening the bowels, dusting a picture on Christmas Day, and sexual intercourse have all preceded rupture in reported cases. A warning haemorrhage may precede catastrophic bleeding, which generally occurs within 48 hours, but there may be no symptoms before rupture, as in Case 2. A bruit was heard in 9%, and a pulsatile tumour was felt in 8% of the reported cases; but, unfortunately, these almost pathognomonic signs are infrequent, and were absent in the five cases here reported.

Haematemesis and melena may follow rupture into the stomach or intestine, and, while Owens and Coffey (1953) state that as many as 30% of patients have these complications, the picture is usually that of frank internal haemorrhage. Often the bleeding is at first retrospective, and this was the case in the only other patient with a ruptured splenic aneurysm that I have seen. I transfused this African patient in a military hospital, but he soon died with massive bleeding.

Before rupture, aortography has been used as an aid to diagnosis (Riemenschneider, 1955; and others). It might be considered meddlesome if a confident diagnosis had been made, but it may differentiate a splenic aneurysm from a calcified echinococcal or splenic cyst, a calcified tuberculous node, or other shadows. Calcification of a tortuous splenic artery, without aneurysm, may also cause confusion without aortography. A confident radiological diagnosis of splenic aneurysm was made in an elderly lady who presented with haematuria, due to a papilloma of the bladder, and a rightinguinal hernia. Cystodiathermy, repair of her hernia, and a laparotomy were done. The cause of the calcification was not found in spite of splenectomy and resection of the whole splenic artery. Fortunately she is none the worse. An aortogram has not been done, and presumably the calcification is still in the body of the pancreas (Fig. 5).

When there are symptoms, confusion with coronary disease and pancreatitis is common. Pancreatitis may also rupture, with diffused pancreatic enzymes in the blood and urine (Colangelo, 1955; Hughes and Joske, 1955).

In pregnancy, concealed accidental haemorrhage is the usual differential diagnosis, but ruptured splenic aneurysm must be borne in mind. Dr. M. E. O'Sullivan, who called the flying squad in to Case 2, had seen the young wife of a fellow British officer in Malaya die after an operation for a ruptured splenic aneurysm in pregnancy.

Treatment

Resection of the artery and splenectomy form the treatment of choice. Double ligation of the artery or resection of the sac has been successful in four cases. Many calcified aneurysms have been treated conservatively, apparently without disaster.

Owens and Coffey (1953), in their authoritative review, state: "At the risk of belabouring the obvious, it may be categorically stated that the treatment of an aneurysm of the splenic artery is exclusively surgical. Once a diagnosis of this lesion is made, or strongly suspected, prompt operative interference is essential." Most other authors endorse this view, and advocate prompt surgery, whether symptoms are present or not. There are indeed still only a dozen survivors reported after rupture.

Lennie and Sheehan (1942) recommend caesarean section in rupture in pregnancy, while Gallagher and Hudson (1954) advise against emptying the uterus, which seems more reasonable. In one report a patient died during the caesarean section undertaken to facilitate the search for the bleeding-point.

Ronen (1953), from the Hague, advises observation provided the aneurysm is "the size of a cherry or smaller," completely calcified except where it joins the main trunk, asymptomatic, and not in a woman of child-bearing age or in a patient with hypertension. According to these criteria, Case 3 would be on the borderline, with an almost completely calcified aneurysm the size of a cherry, but operation was needed in this case for the renal carcinoma, and splenectomy was easily done at the same time. Case 4 merited operation because of the size of one of the aneurysms, quite apart from the carcinoma of the oesophagus, and Case 5 because of the hypertension. Ironically, Ronnen would have advised against operation in the case above, of the smaller "splenic aneurysm" diagnosed confidently by radiology but not confirmed at laparotomy.

A good case can be made for conservatism in the elderly or when the patient is a poor operative risk.

Ronen (1953) states that he could find no case of a ruptured calcified splenic aneurysm in the literature. This is an important point. Some incompletely calcified splenic aneurysms rupture (Tagart, 1952), but often the question of calcification is not specifically mentioned in reports, nor are x-ray films always taken before operation, or of the specimen after operation, or at necropsies, in cases of rupture. Complete calcification can be demonstrated only by detailed anatomical study. Berger et al. (1953), from a study of the literature, state that 35% of splenic arterial aneurysms rupture. It is difficult to assess the number of aneurysms at risk, and also the number that rupture, but this figure seems far too high.

However, until the danger of rupture can be foretold with accuracy, it would be wise to treat all splenic arterial aneurysms with great respect, and, as a general rule, to excise them.
Summary

Five cases of operative removal of splenic aneurysms are reported. In this series there was one death following rupture of an aneurysm, and one recovery after rupture of an aneurysm in a pregnant woman; another patient had a porto-caval shunt. In the three patients with unruptured aneurysms the diagnosis was made by the radiologist before operation, and these patients survived.

I am indebted to Dr. A. B. Hill for the pathology reports; to Dr. E. J. S. Townsend for the radiographs; and to Dr. A. Hegarty, who anaesthetized four of these patients; and to my surgical colleagues, Mr. F. J. Milward, under whose care Case 1 was admitted, and Mr. A. McEwan Smith, who referred Case 5.

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CLINICAL TRIAL OF ACEPROMAZINE MALEATE IN CHRONIC SCHIZOPHRENIA

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A new derivative of the phenothiazine group of tranquillizers, acepromazine maleate ("notensil"), was first given a clinical trial in France by Delay and Pichot (1957), who studied its effect in 11 psychoneurotic out-patients and 20 severe psychotics. The use of acepromazine in other kinds of disorders has already been mentioned by Stafford-Clark (1957), and it was understood that our project was only part of the trials planned in this country into the use of acepromazine in different clinical conditions. The largest single clinical group of diseases with behaviour disturbance in a mental hospital remains schizophrenia, and we decided to limit our study to this disease. Our aims were (1) to ascertain whether treatment with acepromazine is of value in chronic schizophrenic patients with behaviour disorders, and (2) to record the incidence of side-effects and toxic effects.

Methods

We defined chronic schizophrenia as an illness characterized by a disorder of emotion and thought, hallucinations, and behaviour disturbances of more than one year's duration. The patients selected numbered 86—42 in the treatment group and 44 as controls. For various reasons four patients in each group were withdrawn. All had been known to us for at least one year and the diagnosis was agreed upon. Patients with a history of jaundice or evidence of active peptic ulceration were excluded.

Before starting the trial our colleagues agreed to discontinue the use of tranquillizers on schizophrenic patients so that we might observe whether, on withdrawal of these drugs, the patients remained in remission or showed signs of relapse. Those who relapsed were then considered for inclusion in this trial, and if accepted, their clinical, nursing, and psychometric ratings were carried out. Clinical rating was made by one of us (J. F. C.) on the basis of a scale described by Boardman et al. (1956), whilst the nursing staff used the rating scale of Berter and Thorpe (1956). Psychometric assessment with a group of tests designed for psychotic behaviour was attempted, but it has not been possible to include these findings in our paper.

Patients were chosen from any ward in the hospital and allocated to treatment or control groups on the basis of Bradford Hill's (1955) prescribed random order chart. This chart was held by the chief pharmacist, who supplied the appropriate substances in identical containers.

The drug, or placebo, was given orally in tablet form at an initial dosage of 50 mg. three times a day. This was increased by 50 mg. a day until a daily total of 300 mg. (given in three equal doses) was reached on the fourth day. We aimed to maintain the dosage at this level for six weeks, although some modifications had to be made when side-effects were encountered. Only those patients who completed a full course of treatment were included in our series.

The clinical and nursing ratings were carried out at weekly intervals during the six weeks of treatment. At the end of this period an approximate clinical assessment of the efficacy of the treatment was made by classification of the subjects into the following groups: (1) improved (to cover all variations between number and severity of symptoms materially less up to a complete remission); (2) not improved; and (3) worse (symptoms aggravated and behaviour more disturbed).

A further statistical assessment of the changes in clinical and behaviour rating scales was made by means of a test on the differences in the ratings before and after treatment.

Distribution of Clinical Types and Comparison of Groups

The 78 patients taking part in the trial were classified according to clinical groups (Table I).

<table>
<thead>
<tr>
<th>Types of Clinical Groups</th>
<th>Control Group</th>
<th>Treatment Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Paranoid</td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Catatonic</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Mixed</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Hebephrenic</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>38</td>
<td>78</td>
</tr>
</tbody>
</table>

The average age and duration of stay in hospital for each group are shown in Table II.

<table>
<thead>
<tr>
<th>Age</th>
<th>Duration of stay</th>
<th>Control Group</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>44-32 years</td>
<td>13-29</td>
<td>48-18 years</td>
<td>13-25</td>
</tr>
</tbody>
</table>

As all our subjects had been in hospital for over a year it followed that many of them had previously received some kind of physical treatment. The two groups are compared