found to be 150 mg./100 ml. Fluids were immediately restricted by mouth and penicillin was started. No pitting oedema was observed at any time. Daily blood-pressure readings never rose above 150/90. At no time was there clinical evidence of hepatic involvement. The blood count remained normal throughout. The blood urea rose to 245 mg./100 ml. on December 27 and thereafter fell, until by January 7, 1957, it was normal. (Urea concentration test was also normal on January 7.)

By December 30 fluid balance had been re-established and the spleen was no longer palpable. (The glands subsided more gradually, the last disappearing on February 13.) Urine was clear of red cells by December 31, casts by January 11, and albumin and leucocytes by January 21. Glycosuria persisted. A 24-hour specimen of urine contained no acid-fast bacilli on Löwenstein culture. Serum protein electrophoresis still showed a slight decrease in albumin and increase in α_2 and γ globulins on January 7.

Despite courses of penicillin and chlortetracycline the temperature subsided very gradually and did not settle finally until the middle of January.

Test doses of chlortetracycline and penicillin during March gave no reaction, nor did isoniazid or streptomycin.

On March 8, 4 g. of sodium P.A.S. given orally at 10 a.m. was followed by a prickling sensation in the skin during the afternoon. The temperature at 5 p.m. was 100° F. (37.8° C.). 50 mg. of diphenhydramine was given. At 10 p.m. the temperature was 101.8° F. (38.8° C.) and the patient vomited. Diphenhydramine, 100 mg., was then given and the temperature fell to normal. There was a deficit of 40 oz. (1,140 ml.) in urinary output during the next 48 hours. Blood urea was 30 mg./100 ml. The urine contained no albumin.

The patient was discharged home well on April 4.

Discussion

By far the commonest serious complication of P.A.S. therapy is hepatitis, an excellent review of which is given by Hensler *et al.* (1957). Hepatitis usually accompanies a severe allergic reaction characterized by fever, rash with pruritus, sore throat, conjunctivitis, eosinophilia, and enlargement of glands and spleen, or most of these signs.

It was noted by Lichtenstein and Cannemeyer (1953) and Cannemeyer *et al.* (1955) that 0.3% of their patients treated with P.A.S. had reactions of some sort, but in over 3,000 cases none had renal complications. This infrequency is confirmed in the literature reviewed here. P.A.S. remains a comparatively safe drug whose usefulness outweighs the possibility of occasional severe complications.

It is noteworthy that the patient described here took calcium B-P.A.S. for 83 days without mishap. After 35 days of sodium P.A.S. his severe allergic illness developed. Unfortunately, after recovery, a test dose of calcium B-P.A.S. was not tried. All the allergic reactions already alluded to were due to sodium P.A.S. (Cuthbert, 1950; Livingstone and Street, 1950; Jeffery *et al.*, 1952), or P.A.S. itself (Le Melletier, 1950; Mann, 1953; Silverman *et al.*, 1956). Phillips *et al.* (1957) has described three cases in which the patients exhibited allergic reactions to sodium P.A.S. and

were subsequently able to take calcium B-P.A.S. uneventfully. As calcium B-P.A.S. is of comparatively recent introduction, it remains to be seen whether it does in fact reduce the incidence of allergic reactions. Pharmacologically there would appear to be no reason to expect this.

Summary

A review of the literature of renal complications of P.A.S. therapy is given. The frequency of association of renal with hepatic complications is discussed.

A case is described of severe renal failure due to sodium P.A.S. as part of an allergic reaction to the drug. The diagnosis was confirmed by subsequent test doses. The patient made a spontaneous recovery some time after the drug was stopped.

The rarity of renal complications of P.A.S. therapy is mentioned. There would appear to be no indications for using P.A.S. less frequently than is at present the custom.

The possible relationship of P.A.S., sodium P.A.S., and calcium B-P.A.S. to allergic reactions is briefly considered. It is possible that calcium B-P.A.S. is the safest of the group available for routine use at the present time.

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LEIOMYOMA OF OESOPHAGUS

REPORT ON TWO CASES SURGICALLY TREATED

BY

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Leiomyoma is the most common benign tumour of the oesophagus. Until recent years most cases were discovered at necropsy. Lewis and Maxfield (1954) reported 47 surgically treated and 108 post-mortem cases in their collection of 150 cases from the world literature. Whether priority of surgical treatment belongs to Sauerbruch or Ohsawa, it is clear that there has since been a new chapter in the field of practical treatment and consequently an increase in the number of surgical cases. Storey and Adams (1956) collected 110 cases of these tumours surgically treated: 16 before 1948 and 94 from 1948 to 1956.

We do not propose to review the whole literature, as this has already been done recently by several authors. However, the infrequency and the successful operative treatment of leiomyoma of the oesophagus gives us reason to present our two personal cases.

Case 1

A male nurse aged 43 was referred to the E.N.T. out-patient department on June 15, 1956, complaining of dysphagia and retrosternal discomfort when swallowing. He stated that six weeks previously he had an attack of influenza, following which the dysphagia developed. On E.N.T. examination no abnormality was revealed. The chest x-ray examination showed no abnormality, but a barium swallow on June 26 revealed a large well-defined indentation of the middle third of the oesophagus; this was interpreted as probably due to extrinsic pressure; no hold-up of the barium occurred. On August 30 oesophagoscopy revealed only a slight swelling on the posterior wall of the oesophagus at the level of the upper and middle thirds.

FIG. 1.—Case 1. Barium swallow. Note the typical filling defect and the ring or crescent shape of the barium column.

Bronchoscopic examination was negative. A repeat barium-swallow examination again showed the filling defect at the junction of the upper and middle thirds (Fig. 1). The patient was admitted to our thoracic surgical unit on October 22, and in addition to the dysphagia some vomiting occurred after meals. He had also lost a little weight. He had been suspected, about a year previous to the dysphagia, of having a duodenal ulcer. Otherwise he had always been in good health.

On examination he was of normal build; there were no signs of anaemia and no adenopathy. The cardiovascular and respiratory systems showed no abnormality, neither did his digestive system, apart from the dysphagia and vomiting. The abdomen was normal. Blood examination showed no anaemia, and the white-cell count was normal. The ensemble of the history and examination led us to the diagnosis of non-malignant tumour of the oesophagus, probably a leiomyoma.

Operation

On November 7 the oesophagus was explored through a right thoracotomy with the patient in the lateral position. There was no abnormality of the lung or mediastinum, but bulging and swelling of the oesophagus were found just below the arch of the azygos vein. The tumour was 3 to 4 cm. long and quite localized. A vertical incision over the wall of the oesophagus at the level of the tumour was made. The tumour, which was lying between the mucosa and the muscular layers of the wall of the oesophagus, was shelled out readily. The muscle layers of the oesophagus were repaired with fine silk. After drainage of the pleural cavity the thoracotomy wound was repaired.

Histological examination revealed a fibroleiomyoma. There was no sign of malignancy.

The immediate post-operative recovery was uneventful, and after 48 hours the patient started to drink water and then soft drinks, and later took a soft diet. After a further two weeks he was discharged, taking a normal diet, and had no dysphagia or digestive disturbance. Before discharge a barium-swallow examination showed normal passage of the barium and no filling defect. Six weeks after discharge he was very well and in a satisfactory condition. When seen on May 7, 1957, he had no dysphagia, was putting on weight, and his condition was very satisfactory.

Case 2

A schoolmaster aged 34 was first seen in November, 1956. He gave a history of two years' discomfort in the epigastric region, and dysphagia. When this dysphagia first started in 1954 he had a barium-meal examination, which was reported as normal. On questioning, he did not think he had lost any weight.

On examination there was no adenopathy. The cardiovascular and respiratory systems were normal. The abdomen was soft without any tenderness. There was no hepato-splenomegaly or anything relevant in the past history. The barium-swallow examination showed a

FIG. 2.—Case 2. The barium swallow; showing also the soft-tissue mass at the level of the filling defect of the oesophagus.

rounded filling defect in the upper oesophagus at the level of the sterno-clavicular junction. The defect in the oesophagus was smooth and suggestive of extrinsic tumour. Plain chest x-ray films on the lateral view showed a soft-tissue mass in the superior mediastinum (Fig. 2).

Oesophagoscopy at the end of December showed no abnormality. There was the impression of a hard mass pressing into the posterior wall of the oesophagus.

The patient was referred to our thoracic surgical unit with a diagnosis of chondroma or dermoid tumour pressing on the oesophagus.

On admission he gave the same history of dysphagia, and on clinical examination again no abnormality was discovered. The blood count was normal. A barium-swallow examination showed the same filling defect (Fig. 3). From the long-standing dysphagia, the clinical examination, and the typical barium-swallow examination, leiomyoma of the oesophagus was diagnosed.

FIG. 3.—Barium swallow of Case 2. Again the crescent-shaped barium column with a typical filling defect is present.

Operation

The tumour appeared to be at the level of the junction of the upper and middle thirds of the oesophagus. The oesophagus was explored through a right thoracotomy, with the patient in the lateral position. No abnormality of the lung or mediastinum was found, but a fairly large tumour the size of a small orange lay in the wall of the oesophagus at the junction of the upper and middle thirds; the arch of the azygos vein was running over the middle of the tumour. The oesophagus was mobilized after ligation and division of the azygos vein; then a vertical incision was made over the tumour (about 4 cm. long). The incision was through the muscle layers only, and the tumour was shelled out fairly easily. The tumour was lobulated (Fig. 4), the

FIG. 4.—Case 2. Lobulated growth.

mucosa remaining intact. The muscle layers of the oesophagus were then stitched with fine silk, and after insertion of a drainage tube into the right pleural cavity the thoracotomy wound was repaired.

The immediate post-operative recovery was uneventful, and after 48 hours the patient was given water and then soft drinks. A week later he was eating very well on a soft diet. After two weeks he was discharged from hospital. His general condition was then very satisfactory and he had no digestive discomfort or dysphagia.

When seen six weeks after operation he was very well. A barium-swallow examination at that time showed that the barium passed quite normally through the oesophagus, the contours of which appeared to be normal. He later lived abroad, and has written to tell us that he has had no dysphagia and was enjoying his food.

Discussion

Authors who have collected cases of leiomyoma of the oesophagus from the world literature record that most leiomyomas usually occur in the lower and middle thirds of this organ. In our cases they were found at the junction of the upper and middle thirds. The age range of patients is between the third and sixth decades of life. In all series there are more males than females, the ratio being as high as 2 to 1.

Symptoms

1. *Dysphagia*.—Both of our patients complained of dysphagia. Many cases may be asymptomatic—about 50% in the series of Johnston *et al.* (1953). Obviously the presence of symptoms depends upon the size and location of the tumour, as it is of mechanical origin. Dysphagia is the most common symptom, alone or associated with other symptoms. The myoma being a slowly growing tumour, dysphagia may be present for a long time with various degrees of severity. In Case 2 the patient had dysphagia for three years before his operation. Dysphagia may be intermittent, as in our patients, and in the case of Chalmers *et al.* (1951). Most if not all of the oesophageal conditions at one stage or another present the symptom of dysphagia, and even long-standing dysphagia is not very helpful in making the differential diagnosis; this is based on other symptoms and investigations.

2. *Loss of weight* is a relatively unimportant symptom. In spite of long-standing dysphagia in this condition, loss of weight is either absent or very slight. Only one of our patients (Case 1) lost a little weight. The other, in spite of his long-term dysphagia, had not lost weight.

3. *Other Symptoms*.—One of our patients had attacks of vomiting. Epigastric pain and discomfort are often recorded in different series, and even the respiratory disturbances can occur (for example, the patient of Chalmers *et al.* with "respiration bouché").

Physical Examination and Clinical Investigations

Physical examination is usually negative. The blood count and laboratory findings are also usually normal.

Oesophagoscopy usually reveals no lesion of the mucosa. In both of our cases this examination showed no lesion of the mucosa, but the impression of extrinsic pressure. Occasionally ulceration or congestion of the mucosal membrane can be seen (Lortat-Jacob, 1949), and then the biopsy may establish the diagnosis. The value of the oesophagoscopy is to rule out the possibility of carcinoma.

The straight x-ray film of the chest may sometimes show the presence of the mediastinal mass with or without displacement of the trachea. This was the case in one of our patients. The barium-swallow examination, on the other hand, gives the most valuable diagnostic information. Radiological features of benign tumours of the oesophagus and their differential diagnosis from malignant ones have been described by many authors, and Buckstein (1953) discusses the matter fully in his book. Benign intramural tumours of the oesophagus have many common features whatever their histological structures may be. Also, the intramural, submucosal, and extrinsic ones may be differentiated one from another, although at times with difficulty (Schatzki and Hawes, 1942).

The filling defect caused by the tumour mass has a smooth surface, and there is a ring or an arc shadow of the barium column. This filling defect has been referred to by many as the "half-moon" or "lacunar" and "crescent shape." The tumour of the lower end may produce considerable dilatation.

Treatment

Removal of the tumour by surgery is the only method of cure. The enucleation must be considered in every case from the first instant, as most of the leiomyomas can be removed in this way. The operative mortality rate has been recorded to be about 9% on the whole. The rate is lower for enucleation and higher for excision by resection

(Lewis and Maxfield, 1954). Pleural and pulmonary complications have been noted to follow enucleation; also hiatus hernia and oesophagitis when resection has been performed.

Summary and Conclusion

Leiomyomas of the oesophagus were once incidental post-mortem findings, but recently they have usually been diagnosed and removed surgically. In cases of long-standing dysphagia, without loss of weight in young and middle-aged patients, this tumour has to be considered. Investigations, particularly barium-swallow examination, lead to the diagnosis. The diagnosis of the tumour is important because most, if not all, leiomyomas of the oesophagus can be cured by enucleation.

We have presented two cases, pre-operatively diagnosed and surgically treated by enucleation.

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METASTATIC CARCINOMA OF THE PROSTATE AND BLEEDING

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The phenomenon of fibrinolysis and the presence of hypofibrinogenaemia in metastatic carcinoma of the prostate, if searched for, is not infrequent; for example, Tagnon, Whitmore, Schulman, and Kravitz (1953) found six cases showing fibrinolysis in their series of 48. The knowledge of the mechanism of fibrinolysis is still limited, but has been diagrammatically represented by Stefanini (1953). Tagnon *et al.* (1946) state that fibrinolysis is present when the clot of whole blood or diluted plasma disappears completely in less than 24 hours at 37° C. Furthermore, Tagnon *et al.* (1952) believe that the mechanism of fibrinolysis in prostatic cancer may be different—that is, that the prostatic cancer itself may be the source of the enzyme responsible for the dissolution of the blood clot. Huggins and Vail (1943) demonstrated such a fibrinolytic enzyme in prostatic tissue. Ratnoff (1952) demonstrated fibrinolysis and hypofibrinogenaemia in cancer of the head of the pancreas, but he did not think the process was due to release of pancreatic trypsin. McKay *et al.* (1953) described a case of mucinous carcinoma of the body of the pancreas with hypofibrinogenaemia and multiple fibrin thromboses, but did not carry out tests for fibrinolysis.

The relationship between metastatic carcinoma of the prostate and bleeding is of interest in that the bleeding, which may be dangerous (Swan *et al.*, 1957), may be due to fibrinolysis and fibrinogenolysis, or to the more frequent finding of thrombocytopenia secondary to bone-marrow involvement. Clinically, the bleeding sites, which are particularly from the nose and urinary and gastro-intestinal tracts, as well as in the skin or after minor trauma, may be identical. Tagnon, Whitmore, Schulman, and Kravitz (1953) report that the platelet count may be depressed in metastatic carcinoma of the prostate with fibrinolysis, but haemorrhagic manifestations in association with fibrinolysis occur despite the presence of a normal level of platelets.

The following report concerns a case of metastatic carcinoma of the prostate with fibrinolysis, hypofibrinogenaemia, hypoprothrombinaemia, and thrombocytopenia, and the response to stilboestrol therapy; and it is contrasted with another case with thrombocytopenia and bleeding secondary to bone-marrow involvement.

Case 1

A man aged 68 was admitted to hospital on May 10, 1957, complaining of anorexia, loss of weight, and low back pain; immediately before admission he had a brisk rectal haemorrhage, passing about 1½ pints (850 ml.) of bright red blood.

On examination he was pale and ill, with many ecchymoses and purpuric spots over the limbs and trunk. It was noted later that there was moderately severe oozing from venepuncture sites. Rectal examination revealed a hard, irregular prostate and the presence of bright red blood. He had several moderately severe rectal haemorrhages during the first few days after admission and he had to be transfused with four pints (2.3 litres) of whole blood. The blood sent for cross-matching remained in a fluid state, any clot that had originally been present having disappeared on reaching the laboratory.

Investigations.—Radiography showed osteoplastic deposits involving the right innominate bone and lumbar vertebrae. Haemoglobin, 5.1 g./100 ml. (35% Haldane). White blood count, 6,000/c.mm. (polymorphs 65%, lymphocytes 24%, monocytes 1%, eosinophils 1%, myelocytes 2%, metamyelocytes 7%). The blood film showed some macrocytes, occasional megaloblasts, and 24 nucleated red blood cells per 100 leucocytes. Serum alkaline phosphatase, 40 K.-A. units.* Total serum acid phosphatase, 6.3 K.-A. units. Alcohol stable fraction, 3.5 units. Serum bilirubin, 0.6 unit. Thymol turbidity, 0.8 unit. Platelet count (Lempert), 40,000/c.mm. Prothrombin activity (Quick's one-stage), 40% of normal control. Plasma fibrinogen level, 100 mg./100 ml. Whole-blood clotting-time (Lee and White), 6 minutes. Plasma recalcification time, 2 minutes. Capillary whole-blood clotting-time, 4 minutes. Factor 5, no deficiency. Factor 7, no deficiency. Clot retraction test (Biggs and Macfarlane, 1953): the clot was formed in normal time but was gradually lysed, thus rendering the test impossible to carry out.

Test for Fibrinolysis.—A standard fibrin clot was formed from equal quantities of normal plasma, brain thromboplastin, and M/40 calcium chloride at 37° C. The standard clot was washed free from thrombin with physiological saline and was suspended in the patient's plasma and placed in a water bath at 37° C. At the same time controls were set up, using a similar fibrin clot and normal plasma. The fibrin clot suspended in the patient's plasma was completely lysed and disappeared after four hours. Those in the control tubes were intact up to at least 48 hours.

Two-stage prothrombin time (Biggs and Douglas, 1953): true prothrombin was 70% of normal control. Sternal marrow examination: mainly normoblastic but late megakaryoblasts were seen; no neoplastic cells seen. Fractional test meal with histamine showed the presence of free acid. A