clostridial infection, would appear to be most unusual, and, except in diabetes mellitus, is outside our experience.

The combination of vascular disease and neuropathy with severe diabetes evidently can so lower the patient's resistance to infection that organisms which normally possess little virulence can very rapidly invade the limb, starting from a small local lesion such as an ulcer on the foot. It is possible that the increased glucose in the tissue may enhance the gas-production by organisms such as *E. coli*. The rapid multiplication of the bacteria may result in the production of gas in sufficient quantity to be clinically apparent. The ability of this bacillus to produce gas in culture media containing carbohydrate is well known, and a parallel exists in the pneumaturia of diabetes, which has been reviewed by Foord *et al.* (1956), who have suggested a similar mechanism. The accumulation of gas in the affected limb may also be enhanced by the impairment of circulation delaying absorption.

Spreading infection in the limb of a diabetic, whether gas be present or not, requires prompt treatment, and early recognition of the condition is essential. The diabetic neuropathy and possibly the toxaemia appear to minimize the pain usually experienced in acute infections of the limb and also the awareness of other new symptoms; the limb must be repeatedly and carefully examined.

In Case 1, oedema of the thigh without tenderness was the first sign of spread. The spread of crepitus in infection commonly leads to the diagnosis of a clostridial infection. The clinical picture in these cases, however, is more in keeping with that described by MacLennan (1943) of the similar anaerobic streptococcal cellulitis and myositis seen in the Middle East Campaign. The tempo of the infection is slower than that of clostridial infection. Pain is not so marked, toxaemia is slower in onset, and the temperature and pulse are not as elevated. The diagnosis is confirmed at operation. The gas appears maximal in the fascial layers, and the muscle on biopsy is contractile, and, apart from some oedema, is normal in colour. Immediate search for organisms in pus and muscle should be made. Treatment with antibiotics was disappointing in the one case (Case 1) where the organisms were shown to be sensitive by *in vitro* methods to the antibiotics used. Choice of antibiotics may be complicated by uncertainty of the causative organism, as various bacteria may be cultured from the local lesion. In view of this it may be justifiable to give large doses of more than one antibiotic. Early diagnosis and surgery would appear to be essential for success. In Case 4 it was felt that some measure of success had been achieved, as the ultimate cause of death was unrelated to the initial infection.

Summary

Four fatal cases of non-clostridial gas-infections in diabetics are described and the literature is briefly reviewed.

The organisms cultured from these cases were: Case 1, *Str. faecalis* and *Bacteroides varius*; Case 2, micrococci and *E. coli*; Case 3, *E. coli* and anaerobic streptococci; Case 4, *E. coli*.

The effect of diabetes on the production of large quantities of gas and the enhanced invasiveness of organisms which usually are not markedly gas-forming or invasive is discussed.

The insidious onset of pain is noted and the differential diagnosis from clostridial gas-gangrene is discussed. Emphasis is put on the slower tempo and the findings at operation.

Successful treatment is based on early diagnosis.

We thank the consultant staff of the United Bristol Hospitals for permission to examine and report on patients under their care. We are also grateful to Dr. W. A. Gillespie for advice and encouragement in the preparation of this paper.

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ARGENTAFFINOMA OF THE LUNG WITH CARCINOID SYNDROME

BY

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Malignant carcinoid of the small intestine producing a peculiar complex of symptoms known as the carcinoid syndrome is now well recognized, but a similar condition arising in the lung is rare enough to warrant this report, since only six similar cases have so far been published.

The first description of carcinoid tumours was by Lubarsch (1888), followed by Oberndorfer (1907). In 1914 attention was drawn to the possibility that the chromaffin cells of these tumours could constitute an endocrine reservoir, and Cassidy (1930) reported the case of a young man with an abdominal tumour and hepatic metastases, with flushing of the face and a systolic murmur due to pulmonary stenosis. However, twenty years elapsed before a relationship was established between carcinoid tumours and a certain endocrine symptom-complex. In 1952 enteramine, or serotonin, the specific hormone of enterochromaffin cells, had been identified as 5-hydroxytryptamine, and in the next year serotonin was found in carcinoid tumours. In 1955 the degradation product of serotonin, 5-hydroxy-indole acetic acid, was found in the urine of patients with carcinoid tumours, since when the syndrome of the functioning carcinoid has become widely recognized.

The primary lesion is usually in the gastro-intestinal tract, in which event there are invariably hepatic metastases in those cases presenting the carcinoid syndrome. In a series of 50 cases of ileal carcinoid reviewed by Thorson (1958), 10 had an associated carcinoid syndrome and all of these had hepatic metastases.

On the other hand, of 52 cases of carcinoid of the appendix not one had hepatic metastases or evidence of the functioning syndrome.

There have been several reports of the carcinoid syndrome occurring in association with bronchial adenoma. Kincaid-Smith and Brossy (1956) reported a case in which the carcinoid syndrome developed six years after lobectomy for a bronchial adenoma, the symptoms being produced by hepatic metastases. Stanford *et al.* (1958) report a case of bronchial adenoma with a solitary metastasis and associated carcinoid syndrome. Warner and Southren (1958) reported two cases and mentioned two others in the files of the American Armed Forces Institute of Pathology. Schneckloth *et al.* (1959) reported a further case and Freidman presented another to a meeting of the Australasian College of Physicians in Sydney in 1958.

Case Report

The patient was 62 years old in 1952, when she was referred by a suburban hospital with a three-months history of cough and sputum, one small haemoptysis, and the loss of approximately 3 st. (19 kg.) in weight. Apart from diminished expansion of the left hemithorax, no significant clinical signs were noted, but a chest *x*-ray film (Fig. 1) was suggestive of a tumour involving the upper lobe of the left lung, with elevation of the left dome of the diaphragm, which was paretic. Bronchoscopy was performed without any definite disease being seen, and as the patient rejected the suggestion of thoracotomy, and in fact would not agree to any further investigation, she was merely followed in the out-patient clinic, with progressive *x*-ray films of the chest. These showed no change, and the patient's clinical state did not alter until November, 1958, when she complained of pain in the left upper chest and increasing dyspnoea and when *x*-ray examination showed enlargement of the left-upper-lobe opacity with further shift of the mediastinum to the right.

She declined a recommendation of immediate admission, but agreed to enter hospital in the new year, by which time she had become very dyspnoeic and complained of attacks

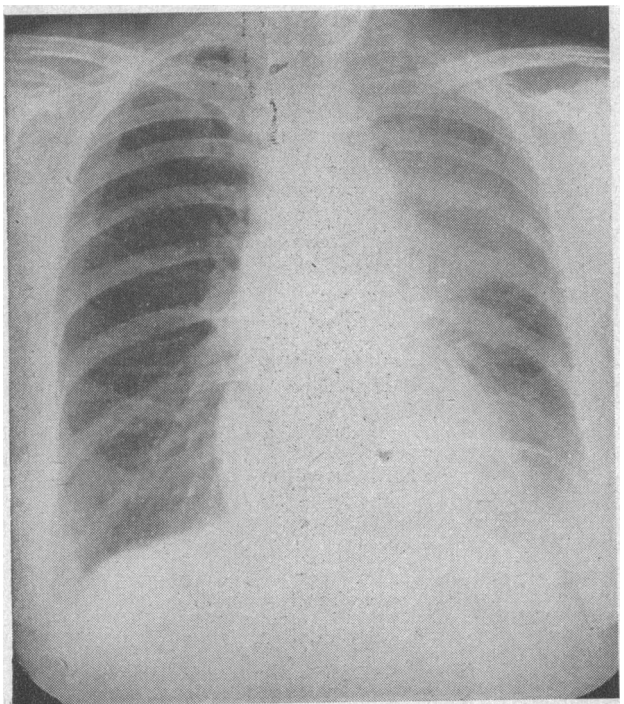

FIG. 1.—*X*-ray film taken on November 11, 1952, suggestive of a tumour involving the upper lobe of the left lung.

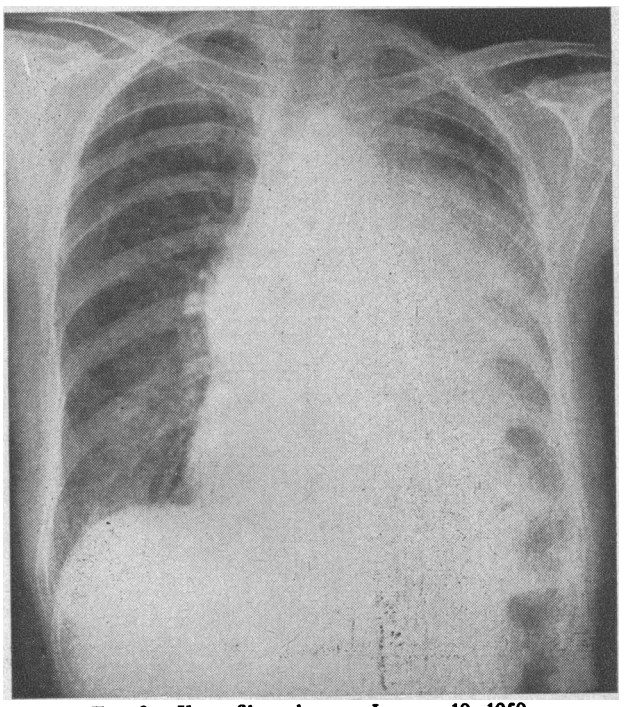

FIG. 2.—*X*-ray film taken on January 19, 1959.

of diarrhoea lasting two or three days, intermittent flushing of the face and upper thorax, and episodes of wheezing. She also had oedema of the legs and a raised jugular venous pressure (4 cm.), these signs subsiding after treatment with digoxin and diuretics. Her chest *x*-ray film was as reproduced in Fig. 2, and subsequently a bronchogram was performed which showed obstruction of the left upper lobe bronchus. At her own insistence she was discharged from hospital at the end of January, but was readmitted in March with recurrence of signs of congestive cardiac failure, there being oedema of both legs, an elevated jugular venous pressure, and hepatomegaly; in addition, there was marked oedema of both hands and forearms, the left more so than the right, and although this fluctuated somewhat it showed no real response to diuretic therapy. Her facies and upper thorax had a dusky cyanotic tint with a number of telangiectases and obvious ecchymoses over both forearms.

At this stage the diagnosis of a functioning carcinoid was suggested and specimens of urine were examined for excretion of 5-hydroxy-indole acetic acid. Daily excretions of 28 to 40 mg. of 5-H.I.A.A. were obtained. After two weeks her hepatomegaly had subsided so that the liver was only just palpable, and a liver biopsy revealed only normal tissue. A basal systolic murmur had been noted on a number of occasions, and an electrocardiogram showed pulmonary P waves but was otherwise normal. She was treated with nicotinic acid 10 mg. b.d., chlorpromazine hydrochloride 25 mg. t.d.s., digoxin 0.25 mg. b.d., and injections of mersalyl twice weekly. Although there was no appreciable change in her oedema, her facial flushing and diarrhoea were greatly relieved. At the request of her relatives she was transferred to a nursing-home, where she died on May 11, 1959.

Post-mortem Findings

The significant portions of Dr. V. J. McGovern's report are as follows.

"*Lungs:* The right lung is very congested and oedematous. The upper lobe of the left lung is entirely replaced by tumour, and this tumour directly invades the regional lymph nodes and has involved the hilar lymph nodes of the right lung. A tongue of tumour projects into the left main bronchus through the main upper-lobe bronchus. On section the tumour is found to have a semi-translucent, white

appearance in some places and a haemorrhagic appearance in others. The heart is normal in all its chambers and valves. There is no lesion present which can be attributed to serotonin. Tumour of the lung is compressing the left pulmonary artery and the pulmonary veins on the left side. *Liver:* The liver appeared normal. *Alimentary Tract:* The appendix had been removed some time in the past, and in the caecum near by there is a secondary carcinoma measuring 1.5 cm. in diameter. There is a further small secondary deposit in the pelvic colon. *Pancreas:* There are several carcinomatous nodules in the head of the pancreas and a small one in the tail. *Adrenals:* Each adrenal gland contains a secondary deposit of tumour, with that on the left side being bigger than the right and measuring 2.5 cm. in diameter.

"*Histology.—Lung:* The tumour is composed of small cells with slightly acidophilic cytoplasm (Fig. 3). The tumour cells tend to be arranged in an alveolar fashion. The

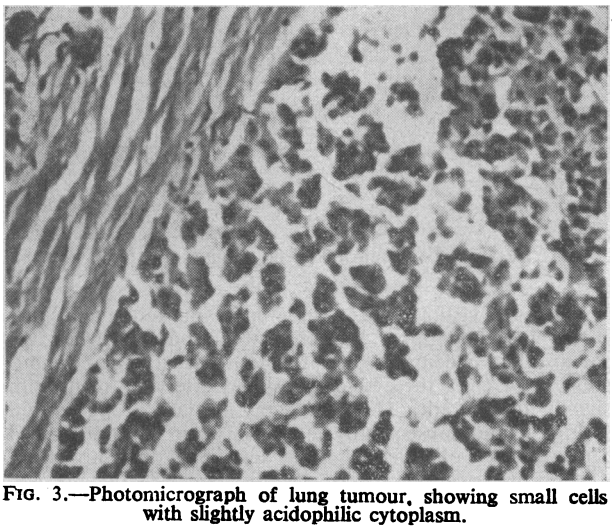

FIG. 3.—Photomicrograph of lung tumour, showing small cells with slightly acidophilic cytoplasm.

tumour in the pancreas and elsewhere has a similar appearance. The tumour does not have any argyrophyl reaction, but this may be due to post-mortem change, the necropsy have been performed 24 hours after death."

Discussion

The diagnosis of carcinoid syndrome depends upon the presence of suggestive symptoms and signs, upon biochemical evidence of excessive production of 5-hydroxytryptamine, and upon histological examination of the primary and metastatic tumours.

Of the clinical features, cyanotic flushes and abdominal symptoms are probably the most common. Although often intermittent, the flushing may be constant and accompanied by telangiectasia or purpura. Diarrhoea and abdominal cramps, with at times the picture of intestinal obstruction, are common. Oedema occurs in the face and arms as well as in dependent parts, and wheezing and dyspnoea are frequent features. Valvular disease of the right side of the heart usually appears late in the course of the illness, with signs of pulmonary stenosis, tricuspid stenosis, or incompetence. In a small number pellagra-like symptoms develop, due to competition by the tumour for dietary tryptophan. In addition there are the clinical signs of the tumour masses, which in most cases include hepatomegaly.

Since the symptoms associated with functioning carcinoid are due to the production of serotonin, which is derived from 5-hydroxytryptophan and ultimately from dietary tryptophan, the finding of an excess of this substance in the blood, or the degradation product 5-H.I.A.A., is clear diagnostic evidence. 5-H.I.A.A. is produced by the action of monoamine oxidase on 5-hydroxytryptamine, and this enzyme is present particularly in the liver and lungs. As a screening test, qualitative estimation of 5-H.I.A.A. can be easily carried out by the Sjoerdsma test. If this is positive then the 24-hour excretion of 5-H.I.A.A. can be estimated; this normally should be between 2 and 9 mg. per 24 hours, but in carcinoid syndrome is mostly between 40 and 2,000 mg.

Histologically, carcinoids are composed of small cells of central nuclei arranged in columns, rosettes, or alveoli. In intestinal carcinoids, granules staining with silver stain can often be demonstrated as in the parent argentaffin cells. The ease of demonstration of these granules diminishes greatly with the time between obtaining and staining specimens, and in the reported cases of functioning bronchial carcinoids no argentaffinity has been demonstrated. Jackson and Konzelmann (1937) consider that bronchial carcinoids are probably derived from neural elements in the bronchus.

In the case here reported most of the features of the carcinoid syndrome were present without hepatic metastases. Since the tumour was in the lung one can assume that 5-hydroxytryptamine was liberated direct into the pulmonary veins and so to the general circulation, where it would exert its endocrine effects before being inactivated by passage through the lungs or liver. This could account for the fact that the symptoms were quite marked despite a level of 5-H.I.A.A. excretion lower than in most reported cases.

The two bronchial carcinoids reported by Warner and Southren (1958) had hepatic metastases. As both these patients had previously had resection of the primary bronchial lesion, either hepatic or extraportal metastases were obviously essential for the production of the carcinoid syndrome. The cases of Kincaid-Smith and Brossy (1956) and of Schneckloth *et al.* (1959) were similar in this regard. Conversely, the case of Stanford *et al.* (1958) had a solitary extrahepatic metastasis. This and the present case indicate that hepatic metastases are not essential to the production of the functioning carcinoid syndrome by bronchial or other extraportal carcinoids. In the case of pulmonary carcinoids without extraportal metastases, right-sided valvular heart disease would not be expected to occur. A systolic murmur was heard at the base of the heart in our case, but at necropsy the valves were normal.

Our thanks are due to Dr. K. Mattocks for the biochemical estimations, to Dr. V. J. McGovern for the necropsy report, and to Mr. Woodward-Smith for the photographic reproductions.

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HYPOTHERMIA AND THE HEART-LUNG MACHINE

CLINICAL APPLICATION OF THE TECHNIQUE

BY

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The concept of combining the heart–lung machine with hypothermia is by no means new. Many workers have combined a degree of hypothermia with their conventional heart–lung circuits, usually with the object of increasing their ability to handle larger patients.

A quite distinct development has been the use of a heart–lung circuit to achieve deep ranges of hypothermia. Notable in this field have been Gollan *et al.* (1955), who first reported extracorporeal cooling to 0° C. in dogs, and more recently there has been the experimental work of Kenyon and Ludbrook (1957). Drew and Anderson's (1959) clinical work has demonstrated the safety and advantages of temperatures around 15–20° C. The use of mechanical pumps in deep hypothermia is to maintain the circulation at temperatures below 30° C. At this temperature and below, the efficiency of the heart as a pump becomes progressively impaired until ventricular fibrillation supervenes.

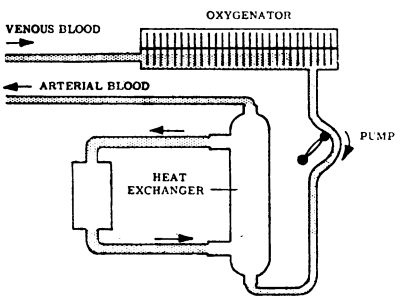

FIG. 1.—Diagram of the circuit used. In clinical use a coronary sinus reservoir and two suction pumps are added.

The use of moderate degrees of hypothermia with the conventional heart – lung machine adds a complication to the apparatus without fully exploiting the advantages of hypothermia. On the other hand, a deep or profound reduction of body temperature, while providing the theoretical ideals of a quiescent heart and dry operating conditions, is hardly applicable in every case in which open heart surgery is contemplated.

Hypothermia offers the possibility of lower flows and reduced priming volumes. In this way blood trauma can be diminished and the ever-increasing burden on the blood banks is relieved.

With the object of providing a more flexible instrument and technique, a hypothermic by-pass apparatus has been designed. It is equally applicable to children and full-sized adults, and provides for short or long periods of by-pass with complete arrest of the circulation if required.

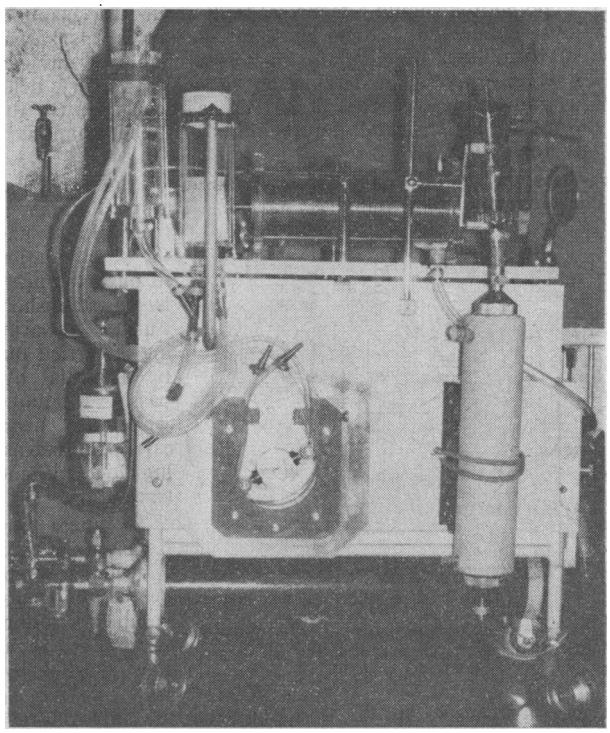

FIG. 2.—Photograph of the apparatus assembled for use.

Apparatus.—Basically the circuit consists of a disk oxygenator (rather smaller than the Kay–Cross variety) and a heat-exchanger made up of thin-walled stainless-steel tubes within an insulated casing (Fig. 1). The priming volume of the machine has been kept to a minimum, and is 3 pints (1.7 litres) for the average case. It is hoped to reduce this further. All blood spilt from the heart and operative field is returned to the circuit by two separate pump lines (Fig. 2). The disks normally rotate at 120 revolutions a minute, but a slower speed-setting is provided. Cooling and rewarming fluids at −4° C. and +45° C. respectively are supplied to the heat-exchanger by a conventional hypothermic apparatus.

Technique

As soon as the chest has been opened, the venae cavae and the femoral artery are cannulated simultaneously. Cooling is then started by a partial by-pass technique—it is in effect similar to the venous cooling method of hypothermia (Ross, 1954), but a proportion of the venous return is taken from the cavae, oxygenated, cooled, and returned to the femoral artery instead of to the venous system.

The initial cooling to 30° C. takes about five minutes. When the myocardium is beginning to flag and the body's metabolic requirements are down to about 50% of normal, the patient's heart is completely by-passed by tightening the vena caval snares. At this temperature it is easy to achieve what amounts to full physiological flows even in adults. A number of possibilities are now available as follows:

1. Further active cooling can be stopped, and a conventional by-pass is then carried out with the advantages of the reduced flow requirements and the added safety factor