minor radio-opacities ranging from phleboliths and arterial calcification to calcified periosteal reactions.

The presence of bone in the base of the ulcer may be a cause for non-healing. In two of our cases in which loose bone was removed more rapid healing seemed to occur on conservative treatment. However, in other cases, where subcutaneous bone was not removed from the ulcer or adjacent areas, healing took place with conservative treatment, surgical measures not being necessary. It is therefore difficult to assess the effect of ossification on healing of a chronic ulcer. The bone may be the cause or the effect of non-healing of the ulcer. The formation of new bone may conceivably be part and parcel of the long-term tissue changes associated with prolonged venous stasis.

The appearances of subcutaneous ossification are pathognomonic (Moberg, 1939; Gray, 1959). This ossification is confined to the subcutaneous layer and produces a coarse network or opacities of bone density in the leg below the knee and above the ankle (Special Plate, Fig. 2). When seen in profile it produces a straight edge, which can be seen to impinge on the subdermal layers. There are definite variations in density within this coarse network, which tends to encircle the leg and occurs most markedly in its middle third. This network of subcutaneous ossification may vary in extent from a small area to relatively widespread involvement. It is easily distinguished from phleboliths, arterial calcification, or periosteal reactions. Though the three latter types of change are often found with varicose veins and may occur with the ossification network pattern, they can easily be recognized. Other radiographic opacities which occur in soft tissues, such as those seen in cysticercosis, guinea-worms, and calcification of the Ehlers-Danlos syndrome, are also quite unlike venous stasis ossification.

The exact mechanism of new bone formation or calcification in soft tissues is unknown, and nothing is known of the cause of ossification in venous stasis. Calcium, phosphorus, and phosphatase levels in the serum and urine are not related to the type of calcification or ossification seen in, for example, venous stasis, non-parasitic cysts of the spleen, thyroid adenomas, or traumatic myositis ossification. In these conditions such investigations are therefore regarded as superfluous. Similarly, it has now been shown in many cases, as well as in the cases described, that these biochemical investi-

gations are invariably negative and can therefore be omitted. The radiological appearance, as described above, is unmistakable and diagnostic of this condition.

The histological changes in and around stasis ulcers have been well documented (Moyer and Butcher, 1955). They include arteriolar and venular luminal obliteration, perineural inflammation, hypertrophy and fibrosis of the dermis, and epidermal atrophy. There may also be lymphatic obliteration, though this is often overlooked. One of the patients in this series presented herself with swelling of the feet and was referred for lymphangiography. She showed "a dermal back-flow pattern" with the initial patent violet-blue injection. This is characteristically present in lymphatic oedema. Subsequently, blocked lymphatics with lymphangiographic dermal backflow and only a single small lymphatic trunk in the greater saphenous drainage area were demonstrated (Special Plate, Fig. 3), in addition to her subcutaneous ossification.

Summary

Eight cases are reported of subcutaneous ossification of the legs in association with chronic venous stasis.

The clinical and radiographic features make a definitive diagnosis possible without recourse to biochemical investigations.

Venous stasis subcutaneous ossification may occur in males as well as in post-menopausal females and has been seen in the absence of fungal infection, contrary to previous reports. Peripheral oedema and lymphatic occlusion, on the other hand, is an occasional associated feature.

We are grateful to Mr. George Qvist, Senior Surgeon at the Royal Free Hospital, for permission to include Case 2. We are also indebted to Mr. Stanley Lee and Dr. B. Strickland, of the Westminster Hospital, for allowing us to include Case 3. We thank Mr. R. R. Phillips, of the Photographic Department of the Royal Free Hospital, for help with the illustrations.

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Preliminary Communications

Oxygenation of Cats by Hydrogen Peroxide during Temporary Ventilatory Arrest

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Cyanosis in patients with congenital heart disease is due to a shunt of desaturated blood from the right side of the heart into the arterial circulation, and this mechanism may also contribute to hypoxaemia in many forms of pulmonary disease. This shunt blood is not exposed to the ventilating surfaces of the lung, and its oxygen content cannot therefore be affected either by increasing the alveolar ventilation or by increasing the partial pressure of oxygen in the lungs. The only improvement in oxygenation to be expected by these measures will be from oxygen dissolved in the plasma in that portion of the cardiac output that takes no part in the shunt. A study of alternative methods of oxygenation has led to the present investigation of the use of hydrogen peroxide, infused intra-arterially, to provide an auxiliary means of oxygenation.

If hydrogen peroxide was infused slowly into the aorta during ventilatory arrest, it was anticipated that in the presence of catalase this would release micro-bubbles of oxygen which would accumulate in the lower part of the body. A high partial pressure of oxygen in these tissues would then occur. Desaturated arterial blood in this region would become saturated with oxygen as it passed into the venous system. In this way the blood returning to the heart in the inferior vena cava would be fully saturated with oxygen. The oxygen tension in the inferior vena cava should be capable of being controlled by varying the rate of the infusion and thus kept below that partial pressure at which spontaneous bubble formation occurred. When the infusion was stopped any bubbles trapped in the capillary bed of the hind limbs would dissolve spontaneously as the oxygen tension in the tissues fell. To test the validity of this hypothesis a preliminary experiment was carried out with 14 cats. They were anaesthetized and then subjected to ventilatory arrest to produce an extreme degree of hypoxaemia.

It has proved possible in these circumstances to supply sufficient oxygen by means of hydrogen peroxide to maintain life

in the anaesthetized cats for up to one hour. It is probable that the mode of action is more complex than originally envisaged. This preliminary report presents our experience with the technique and the difficulties and limitations encountered.

METHOD

A high level of circulating catalase is essential for the breakdown of hydrogen peroxide. In the absence of sufficient catalase methaemoglobin is formed after the addition of very small quantities of hydrogen peroxide. There appears to be a quantitative relation between the level of catalase and the amount of hydrogen peroxide that can be broken down without methaemoglobin formation. The methaemoglobin should eventually revert to haemoglobin if given sufficient time (Lück, 1957). The cat was selected for these experiments as it has a higher level of catalase than any other readily available experimental animal. The catalase activity (Kat. f) in cats' blood varies between 16 and 27 units, as compared with human blood, which is usually in the range of 24 to 36 units (Lorincz *et al.*, 1948). *In vitro* experiments confirmed that hydrogen peroxide did not produce methaemoglobin when added to cats' blood, when 3% v/v. concentration was used. The same result was obtained with human blood. It was also confirmed that, *in vitro*, the addition of hydrogen peroxide did not produce detectable haemolysis.

FIG. 1.—Positions of the catheters.

FIG. 2.—Area perfused by hydrogen peroxide.

This catheter was used for withdrawing venous samples from the inferior vena cava. A left femoral-arterial catheter was introduced so that its tip was estimated to be in the thoracic aorta. This level had previously been established as being most satisfactory for the infusion of the hydrogen peroxide. If the catheter was in the low abdominal aorta difficulty was experienced in controlling the oxygen tension in the venous blood. Placing the catheter in the thoracic aorta ensured that the liver was included in the perfused area. The left common carotid was cannulated for arterial sampling and for recording the blood-pressure. In all the cats the tip of this catheter was inserted to the level of the arch of the aorta, its position being

subsequently confirmed at post-mortem examination. Fig. 1 shows the positions of the catheters; Fig. 2 illustrates the area perfused by the hydrogen peroxide. The blood-pressure and the electrocardiogram were continuously monitored. The partial pressure of oxygen in the carotid artery and the inferior vena cava were intermittently measured with an Astrup oxygen electrode. Arterial pH and P_{aCO_2} and base deficit were determined by means of the Astrup pH meter.

The hydrogen peroxide solution was made up to 3% v/v. concentration. This is capable of releasing 10 ml. of oxygen for every ml. of the solution infused. The hydrogen peroxide was infused into the femoral artery by means of a Watson-Marlow pump which had been previously calibrated. Infusion rates of between 0.25 and 1.2 ml. per minute were used.

When cannulation was completed, heparin, 1,500 units/kg., and pentolinium tartrate, 0.7 to 1 mg./kg., were administered. The pentolinium tartrate was given in an effort to limit the vasoconstricting action of the high oxygen tension upon the arterioles. In this dose it failed to produce a fall in arterial blood-pressure below 100 mm. Hg systolic. When satisfactory levels of ventilation and blood-pressure had been established the infusion of hydrogen peroxide was cautiously started. This produced a slow rise in venous oxygen tension and usually an even slower rise in arterial oxygen tension to about 160 mm. Hg. Once this had become stabilized the ventilation was either reduced or stopped and the rate of infusion of the hydrogen peroxide increased. The infusion rate was adjusted according to the arterial oxygen tension. A 3-kg. animal required 0.8 to 1 ml. of hydrogen peroxide per minute, corresponding to 8 to 10 ml. of oxygen per minute. It proved rather more difficult than anticipated to maintain a steady arterial tension. Repeated arterial sampling and adjustment of the infusion rate were required to prevent the arterial oxygen tension from exceeding 200 mm. Hg. Above this level spontaneous bubble formation occurred, producing a damped arterial-pressure trace and then ischaemic E.C.G. changes and hypotension.

Unfortunately the necessity for repeated blood-sampling reduced the blood volume and the oxygen-carrying capacity of the blood. This, together with the concomitant reduction in the catalase, made it progressively more difficult to maintain a stable oxygen tension. Fig. 3 shows the results obtained in one of the

FIG. 3.—Results of perfusion of hydrogen peroxide in a cat.

cats. The behaviour of the venous oxygen tension was at first surprising. It showed only an approximate relation to the arterial tension and was often lower than that in the carotid artery. If the venous oxygen tension rose above 180 mm. Hg there was invariably bubble formation, which usually led to cardiac failure and death. During the respiratory arrest it was usually necessary to administer gallamine in order to prevent spontaneous respiration.

The ventilatory arrest produced considerable acidemia, which was limited by the use of trihydroxymethylaminomethane. In a few animals sodium bicarbonate was used to

correct the pH changes, the effect upon the excess base being ignored. The severe anaemia and the appearance of methaemoglobin in some of the cats prevented any attempts to allow the animals to recover, although spontaneous ventilation was occasionally re-established. In one animal the oxygen-carrying capacity of the blood was so reduced as a result of the experiment that ventricular arrhythmias and ventricular tachycardia developed when the animal was ventilated with room air. This was reversed and the blood-pressure improved when the hydrogen peroxide infusion was restarted.

DISCUSSION

From these preliminary experiments it would appear possible to use hydrogen peroxide to supplement or, for limited periods, to replace pulmonary oxygenation.

The original concept of the blood receiving oxygen as it passes through the tissues is only partially true. It cannot explain why the blood-oxygen tension should frequently be higher in the carotid artery than in the inferior vena cava. The probable explanation is that once a high tissue-oxygen tension is established there will be a pressure gradient for oxygen passing backwards up the aorta in the opposite direction to the actual blood-flow.

The development of methaemoglobinaemia in some of the cats after ventilatory arrest for one hour is surprising. *In vitro*, the blood is able to hydrolyse far greater quantities of hydrogen peroxide without forming methaemoglobin. In some of these animals the infusion had been running for two or more hours and the catalase activity of the blood must have been reduced by repeated blood-sampling. This complication would be unlikely to occur in humans with the slower infusion rates that would be required if the technique were used to supplement pul-

monary oxygenation. It would also be unlikely to occur with the high catalase level present in human blood.

Many of the cats died eventually from the effects of oxygen embolism. The hydrogen peroxide infusion releases micro-bubbles of oxygen into the circulation. They are removed by combination with reduced haemoglobin and, to a small extent, by physical solution in plasma, thus preventing oxygen embolism.

Repeated blood-sampling in these preliminary experiments reduced the oxygen-carrying capacity of the blood. This demanded progressively more delicate control over the infusion of hydrogen peroxide if oxygen embolism was to be avoided. It is anticipated that blood transfusion may overcome this problem in future experiments.

SUMMARY

Cats have been kept alive for periods up to one hour in the absence of pulmonary ventilation by an infusion of hydrogen peroxide into the thoracic aorta. The difficulties experienced with this method of oxygenation are presented.

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Medical Memoranda

Intestinal Strangulation Complicating Familial Mediterranean Fever *

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- * Short-lived febrile episodes accompanied by peritonitis, pleuritis, or arthritis constitute one of the typical characteristics of familial Mediterranean fever (Mamou and Cattani, 1952; Heller *et al.*, 1958; Sohar *et al.*, 1961). Most common are the abdominal attacks. These occurred with variable frequency in over 97% of the 470 patients under our observation, and indeed have become the striking hallmark of the disease. The rapid subsidence of symptoms and signs of peritoneal irritation and the lack of any features referable to the abdomen between attacks, even in patients who have experienced hundreds of such episodes, led us to stress their innocuous nature and to warn against surgical exploration. This in spite of the fact that peritoneal adhesions were often encountered at laparotomy (Priest and Nixon, 1959) and at necropsy in familial Mediterranean fever patients who succumbed to amyloidosis (Heller *et al.*, 1958)—the second typical feature of the disease (Heller *et al.*, 1961).

The purpose of this paper is to record the cases of two familial Mediterranean fever patients who recently died of intestinal strangulation, and to discuss the diagnostic implications.

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CASE 1

The patient, a boy aged 11 at death, was born in Morocco. His brother was affected by familial Mediterranean fever with amyloidosis.

At the age of 7 the patient underwent appendicectomy in Morocco because of an "acute abdomen." Since then he has had numerous attacks of fever and abdominal pain, lasting up to 24 hours, as well as attacks affecting joints. In late 1964 he was admitted to the Zahalon Government Hospital for acute pericarditis (to be reported separately by physicians from the Zahalon Hospital). During this and a subsequent admission in January 1965 thoracic, abdominal, and joint attacks were observed. Physical examination was negative except for a palpable spleen. Urinalysis was unrevealing.

Several months later, while he was at home, fever and abdominal pain again occurred, accompanied by severe vomiting. When these failed to subside, after four days, he was brought to the Zahalon Hospital. Examination revealed stupor, pallor, and marked dehydration. The abdomen was distended, soft, and mildly tender; peristalsis was absent. The rectal ampulla was empty. Insertion of a rectal tube failed to produce flatus. While being prepared for emergency laparotomy he died.

At necropsy the ileum was distended proximal to a section 10 and 20 cm. from the ileo-caecal valve, where two fibrous bands constricted the intestinal lumen. Here the intestinal mucosa and serosa were pale, though proximally the wall was thickened and acutely inflamed; the dilated lumen contained bloody, murky fluid. Distally, the intestine appeared normal. The spleen was enlarged, weighing 190 g. On microscopical examination the proximal portion of the ileum showed an acute inflammatory infiltrate and oedema of the synovia and mucosa. Polarization microscopy of numerous Congo-red-stained histological sections of all organs failed to reveal any evidence of amyloidosis.