with congenital non-spherocytic hemolytic anemia. We have studied two unrelated patients with this disease, employing the techniques described. Erythrocyte glucose-6-phosphate dehydrogenase activity and pyruvic acid kinase activity were normal in these patients. In the erythrocytes of these patients, P^{32} appeared in ATP, IP and 2,3-DPG in a manner similar to that found in normals. However, in contrast to the normal, these cells contained high concentrations of fructose-1,6-diphosphate prior to incubation, which further accumulated and became radiolabelled during incubation.

Since fructose-1,6-diphosphate also accumulates in red cells when glycolysis is inhibited by iodoacetate or sodium fluoride, it is suggested that the accumulation of fructose-1,6-diphosphate in the erythrocytes of patients with congenital non-spherocytic hemolytic anemia indicates an interference with normal glucose utilization at a level below that of the hexose phosphates.

CASE REPORT

Pericardial Fat Necrosis

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NECROSIS of pericardial fat has recently been recognized as an unusual cause of chest pain; difficulty may be experienced clinically in distinguishing this disorder from the many different conditions that cause severe chest pain and collapse. Further difficulty may arise when, following the episode of chest pain, abnormal shadows appear in the radiograph of the chest which pose the usual problems in the differential diagnosis of intrathoracic and mediastinal masses. The diagnostic problem will be solved following thoracotomy and resection of the mass, but the question of the etiology and pathogenesis of necrosis of adipose tissue in this site remains unsettled. The following case illustrates the clinical picture and the pathological changes that are seen in this condition. It is the sixth case so far reported.[1-3]

S.S., a 40-year-old white male, was admitted to the Victoria General Hospital on July 21, 1960, and discharged on August 5, 1960. Chest pain of increasing severity had been present for one week before admission. Two weeks earlier and prior to the onset of pain he had done much heavy lifting because of a temporary change in occupation. The day before his illness began he noticed "some strain" in his chest while pitching horseshoes. On the evening of July 17, one week before admission, he noticed severe pain in the chest beginning gradually in the left precordium and spreading to the axilla. This distress was more or less constant during the week, until the morning of July 21, when an episode of shortness of breath occurred. This was accompanied by more severe chest pain relieved slightly by sitting down and resting. The pain persisted all day, becoming more severe in the evening; at this time he called his physician who sent him to hospital at once.

There had been no significant previous illnesses. He had noticed some epigastric distress a few years earlier but this was relieved following dieting and loss of weight.

Physical examination.—The patient was a sturdy, well-nourished white male who was able to lie flat in bed without distress. He had an elevation of temperature to 99.8° F. at the time of admission. The lungs were within normal limits. Blood pressure was 130/90 mm. Hg, and the pulse rate was 76 per minute with regular rhythm. The heart sounds were of good quality, and there was no murmur or friction rub. The apex beat was not displaced, and there was no clinical evidence of cardiac enlargement. There was an area of exquisite tenderness two fingerbreadths lateral to the left mid-clavicular line in the fifth intercostal space. The abdomen and the nervous system were within normal limits.

Laboratory investigation.—A urinalysis was negative. Hemoglobin was 14.5 g. per 100 c.c. Serum glutamic oxalacetic transaminase (SGOT) was 20 units on each of the three days following hospital admission. An electrocardiogram was within normal limits.

A radiograph of the chest showed a clear right lung field. In the left lung field there was a soft tissue mass measuring approximately 7.0 x 4.5 cm.; it was continuous with the cardiac silhouette at the lower part of its left border in the postero-anterior projection, and was lying anteriorly as seen in the lateral projection (Figs. 1 and 2). Previous chest films made as recently as April 1960 showed no abnormality. Radiographic examination of the upper gastrointestinal tract was normal.

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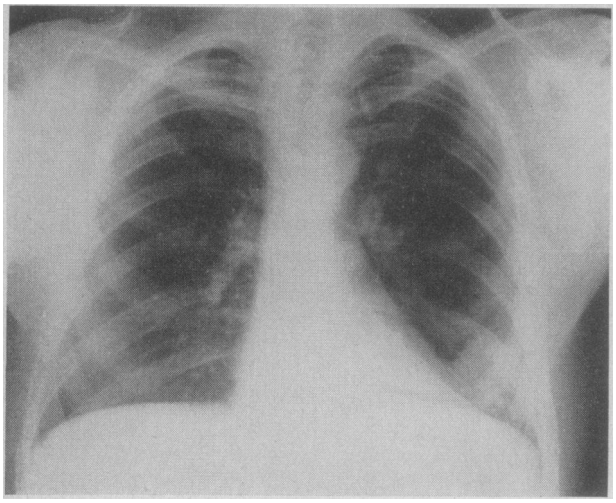

Fig. 1.—Preoperative radiograph of the chest showing an ill-defined opacity in the lower part of the left lung field, lateral to the cardiac shadow.

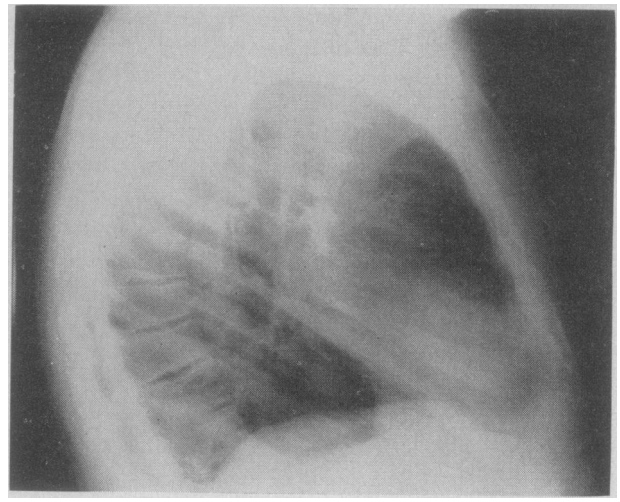

Fig. 2.—Lateral radiograph of the chest showing the anterior location of this soft tissue shadow.

Course in hospital.—Injection of 2% procaine hydrochloride (Novocain) into the area of maximum tenderness of the thoracic wall resulted in complete relief of pain for a period of 1½ hours. It was felt that the patient had not suffered a myocardial infarction. The diagnosis was considered to be paracardiac cyst, and he was discharged to return in one month for evaluation and possible thoracotomy.

He was admitted to hospital again on September 5, 1960. During the period between hospital admissions the patient was never completely free of chest pain. He had a constant ache in the left side of the chest with occasional sharp pains caused by sudden twisting movements, bending or heavy lifting. Physical examination was unchanged. There was no evidence of pleural or pericardial friction rub. A second radiograph of the chest showed no change in the appearance of the paracardiac shadow.

On September 14, 1960, an exploratory thoracotomy was performed. The distal part of the lingula was found to be adherent to a hard walnut-sized mass adjacent to the pericardial sac and attached to the fibrous pericardium. The mass was excised together with surrounding adipose tissue. After the operation, convalescence was delayed by the development of an urticarial skin rash.

Postoperative blood analyses showed that the serum amylase was 58 units (Sömögyi) and the serum lipase was 0.43 units (Cherry-Crandall).

Pathological examination.—The specimen consisted of a lobulated fragment of adipose tissue weighing 20 g. and measuring 7.5 x 5.0 x 4.5 cm. It was moderately firm and indurated in the centre and on section there was an irregular firm area 3.0 cm. in diameter that had a yellow, granular opaque appearance with radiating whitish-yellow strands extending into the grossly normal adipose tissue.

Microscopically, the tissue showed lobulated areas where there was necrosis of fat cells, leaving only the ghost outlines of the cells with no nuclei (Fig. 3). Peripheral to these areas, there were many foamy macrophages and fatty cysts. These cysts were larger than normal fat cells and surrounded by giant cells of foreign body type (Fig. 4). Around this there were bands of fibrous tissue with scattered infiltrations of lymphocytes. In the dense fibrous tissue there were many blood vessels showing adventitial fibrosis but no intimal thickening. The necrotic areas failed to take up oil red O stain in frozen sections, in contrast to the surrounding normal fatty tissue which was heavily stained. Staining for hemosiderin showed granules of iron pigment in the macrophages around the fatty cysts, in the foreign body giant cells and particularly in the fibrous septa around the areas of necrosis.

DISCUSSION

The five previously recorded cases are similar to this one in many respects. The sudden onset of symptoms in these patients would suggest the rapid development of the process that leads to necrosis of fat. Presumably the sudden pain is due to exudation of fluid or blood causing distension of tissue spaces and tension on sensory nerves. It is unlikely that necrosis of fat cells or fibrosis is present initially or that these changes could account for the severe pain.

Experimental studies of fat necrosis have shown that the mechanism of production in adipose tissue begins with an initiating factor that damages the cell membrane leading to the liberation of amylase, lecithinase or both from the cell membrane and cytoplasm.[4] This is followed by digestion of cell fat by intracellular enzymes. The lipid vacuoles, lipophages and foreign-body giant cells, the fibrosis and vascular thickening represent the end stages of the reparative phenomena that follow necrosis. The problem is to determine what initiates the process causing destruction of the membranes of fat cells in the pericardial adipose tissue.

It is well known that acute hemorrhagic pancreatitis may be associated with fat necrosis at distant sites such as the bone marrow, mediastinal fat and subcutaneous fatty tissue.[5] [6] It is unlikely that necrosis of pericardial fat would be present in the absence of overt pancreatic disease, or be

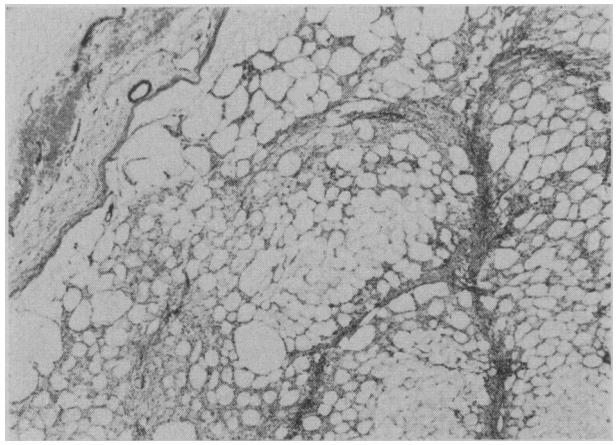

Fig. 3.—Photomicrograph of the area of fat necrosis (centre) with surrounding lipophages, fatty cysts and band of fibrous tissue (left). (Hematoxylin and eosin, original magnification × 25.)

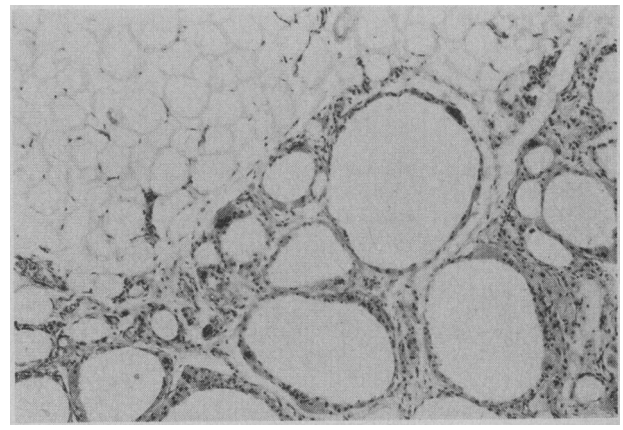

Fig. 4.—High-power view of the fatty cysts with surrounding lipophages and foreign body giant cells. (Hematoxylin and eosin, original magnification × 100.)

confined to one site as was the case in this patient. Although the patient had a history of abdominal distress and previous obesity, there was no clinical evidence of pancreatic disease, such as steatorrhea or diabetes. Estimations of serum lipase and amylase were within normal limits two weeks after operation.

It has been suggested that the lobulated pattern of the involved adipose tissue and the presence of large blood vessels indicate the possibility of a pre-existing structural abnormality of the adipose tissue such as a lipoma or hamartoma.[3] Such a structure, it is postulated, would be particularly vulnerable to the trauma of the beating heart and moving diaphragm. This hypothesis is difficult to disprove, but it appears more likely that the structural changes are a consequence of the inflammation following necrosis and that the fibrosis and vascular thickening are secondary in nature.[1] It is unlikely that the force of the beating heart would lead to rupture of cell membranes and release of enzymes.

The third possibility is suggested by the history of onset of the pain during or after the lifting of heavy objects.[2] During the performance of such an act there is often forced expiration against the closed glottis, in effect a strong Valsalva maneuver.[7] In this situation, certain alterations in intravascular pressure are known to occur. Venous pressure rises rapidly, sometimes as high as 400 mm. of water, and this is accompanied by an initial fall in cardiac output and arterial pressure. Later, when venous pressure falls, there is a momentary increase in systemic arterial pressure. These rapid changes in intravascular pressure might, in exceptional circumstances, cause hemorrhage into the loosely supported adipose tissue of the pericardium. This hemorrhage could be the initiating event in fat necrosis. That such an event may occur is indicated by the finding of hemorrhagic changes in a patient on whom operation was performed 13 days after the onset of symptoms.[2] In the present case, the presence of hemosiderin in the area of fat necrosis suggests previous hemorrhage. It is unnecessary to postulate ischemic necrosis of fat due to organization of the hemorrhage if the hypothesis of the mechanism of fat necrosis, proposed here, is accepted and can be shown to be responsible in this situation.

SUMMARY

A case of fat necrosis of pericardial adipose tissue is described. This is the sixth such case to be reported and is similar in most respects to those previously recorded. The clinical history and examination of the excised specimen of necrotic adipose tissue suggest that the necrosis follows hemorrhage that may be due to the strain of heavy lifting.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

SUAVITER IN MODO

The Quebec provincial board of health never errs on the side of severity. For several months it has been known that small-pox was prevalent in the villages and country, and that many municipalities were doing nothing to check the disease. In those places small-pox is regarded as a trifling, or inevitable, condition against which remedial or preventive measures are either unnecessary or unavailing, according to the view which is adopted. Indeed, to be *bien picotte* is considered in some circles of society as an enhancement of manly beauty.

The inspectors have returned from a visit to the infected districts, and the reports which they bring in are alarming. Whilst it is quite true that the type of disease is mild, it is also true that mild cases often give rise to furious epidemics.—Excerpt from editorial, *Canad. Med. Ass. J.*, 2: 137, 1912.