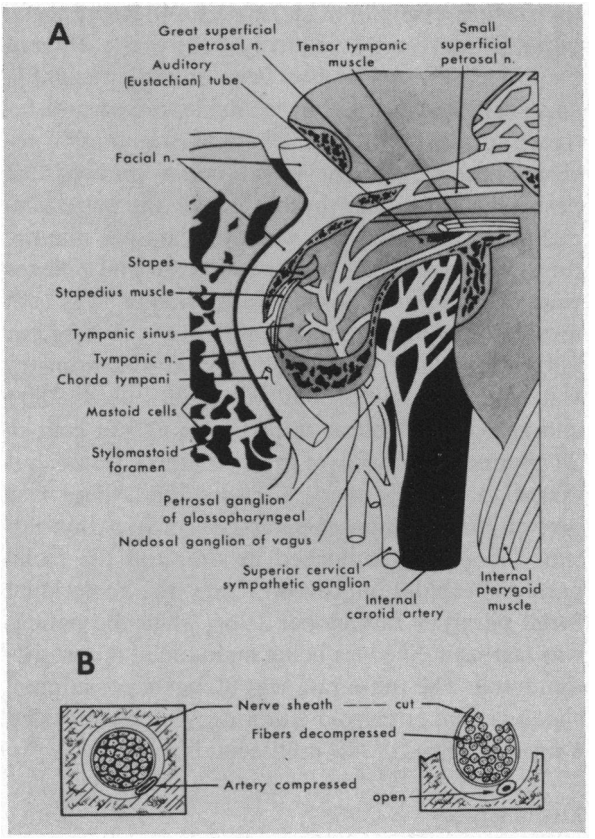

Figure 1.—*A*, Right facial nerve within the skull. From Morris' Human Anatomy, B. J. Anson, copyright 1966, Blakiston Division, McGraw-Hill Book Co. Used by permission. Modified from the original. *B*, Schematic illustration of facial nerve before and after decompression (Case 1).

incision of the transverse carpal ligaments revealed an edematous, noninflammatory thickening of the flexor synovalis about the nerve. In Case 1 herein reported, the ballooning of the facial nerve from its sheath during surgical operations suggests a similar problem with edema and swelling.

Summary

Two hypothyroid patients in whom reversible facial paralysis developed are reported. This association has not been previously emphasized. The anatomical course and confinement of the facial nerve make its situation similar to the median nerve's confinement in the wrist; both may be vulnerable to the profound metabolic and soft-tissue changes of hypothyroidism. Prompt recognition and treatment of the associated hypothyroidism should offer the best chance for complete recovery.

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Subcutaneous Fat Necrosis With Acute Hemorrhagic Pancreatitis

A Case in a Child with Steroid-Resistant Nephrosis Treated with 6-Mercaptopurine

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PANCREATITIS has frequently been described in steroid-treated patients who come to autopsy.* The histologic process is frequently mild and is an incidental finding, pancreatitis not having been manifested clinically.[2,4,12,15,22] The following case report illustrates the occurrence of clinically inapparent acute hemorrhagic pancreatitis in a six-year-old Negro boy with steroid-resistant nephrosis. The pancreatitis was associated with massive disseminated fat necrosis which extensively involved subcutaneous tissues. A final complication in this patient was generalized fungal infection.

Report of a Case

The patient, a six-year-old Negro boy, was admitted to Childrens Hospital of Los Angeles with

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*Reference Nos. 2, 4, 12, 15, 22.

a diagnosis of nephrosis. He had been in good health until chicken pox developed three and a half weeks before admission. A few days later periorbital edema developed, followed by generalized swelling which disappeared without specific therapy. The patient then remained asymptomatic for one week but peripheral edema recurred and he was referred to Childrens Hospital.

On physical examination mild periorbital and pretibial edema were noted. No other abnormalities were observed. Blood pressure was 100/70 mm of mercury.

A hemogram was within normal range. The erythrocyte sedimentation rate was 117 mm in one hour (Westergren method). The specific gravity of the urine was 1.033 and there was a 4-plus reaction for protein. On microscopic examination there were 3 to 7 leukocytes, 5 to 10 erythrocytes and rare hyaline cases per high power field. Blood urea nitrogen was 10 mg per 100 ml, albumin 1.7 gm, globulin 2.9 gm and cholesterol 462 mg per 100 ml.

Treatment consisted of prednisone, 75 mg per square meter of body surface per day. Diuresis occurred and by the eleventh hospital day proteinuria had disappeared. The same dose of prednisone was then given four days a week but relapse occurred six weeks later. Treatment consisting of daily prednisone, 75 mg per square meter a day, spironolactone and chlorothiazide resulted in a clinical remission of five days' duration. The patient then gained 10 pounds in two days and he was thereafter in the hospital for eight and a half months. Daily administration of chlorothiazide, spironolactone and prednisone was continued and led to transient weight loss. Subsequently the patient had no response to corticosteroids or diuretics. By the end of the second month there was pronounced ascites and the patient complained of vague abdominal discomfort. A culture of fluid drawn from the abdominal cavity grew no organisms. Once during the fourth hospital month the child fainted and vomited while being photographed. The drugs being given at the time were prednisone and ACTH. Blood pressure was 100/30 mm of mercury and serum chemical values were: Sodium 107 mEq and potassium 4.9 mEq per liter, calcium 9 mg and phosphorus 5.1 mg per 100 ml. Subjective improvement followed oral sodium chloride supplementation. Later that month the blood pressure rose to 150/100 mm of mercury and the patient complained of diffuse abdominal pain. At that time serum calcium was 7.5 mg and phosphorus was 5.3 mg per 100 ml. The child also spoke of transient hyperalgesia and pruritis of the shoulders, but no abnormalities were evident on inspection. During the sixth month, while the patient was still receiving spironolactone, chlorothiazide and prednisone (5 mg three times a day) a 40-day course of 6-mercaptopurine was begun. There was no diuretic response. The number of leukocytes in peripheral blood fell moderately, erythroid activity of the bone marrow became slightly depressed and the drug was discontinued.

Coincidental with the last few days of mercaptopurine therapy, exquisitely tender, indurated pruritic erythematous lesions appeared over the thorax, and spread rapidly to the buttocks, back and extremities. Cellulitis was suspected and the patient was treated with penicillin and streptomycin. Leukocytes numbered 11,900 per cu mm with 79 per cent neutrophils. Blood cultures were ster-

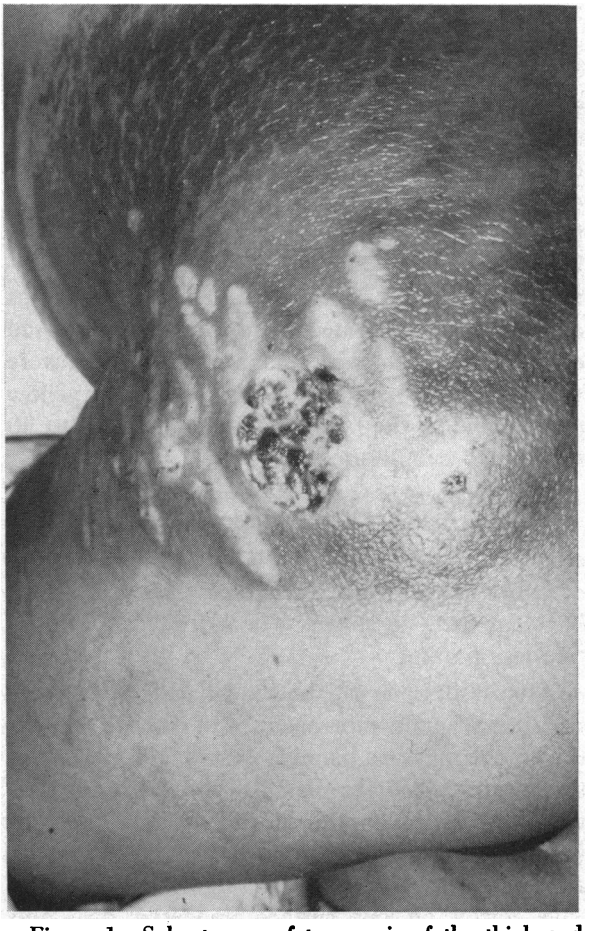

Figure 1.—Subcutaneous fat necrosis of the thigh and back with ulceration surrounded by increased pigmentation.

ile. Within 10 days the painful skin lesions had become vesiculated along the crease lines and striae. Subsequently the vesicles coalesced and ulcerated; thick yellow material oozed from these areas (Figure 1). Pigmentation and superficial desquamation later took place over the back. Exquisite and tender pruritis continued. Numerous cultures of the skin, oral cavity and feces grew candida albicans, but blood cultures remained sterile. Gradually the patient became febrile and leukocytosis appeared.

Two weeks before he died, a grand mal seizure associated with serum calcium of 5.6 mg per 100 ml occurred. Subsequently, oliguria, Cheyne-Stokes respirations, recurrent tetany and prolonged hypotension developed and terminated fatally.

Pathologic Findings

At autopsy, anasarca, a Cushingoid configuration and poor nutritional state were noted. The skin lesions involved thorax, abdomen, back and extremities. The largest ulcers on the back were 40 cm across. The skin along folds appeared elephantiatic, with deeply indurated subcutaneous tissues. The lesions were massively ulcerated and had dirty necrotic bases. In all the appearance was that of a third degree burn which had become badly infected. Hydrogen peroxide application to ulcer bases resulted in bubbling. Bullae 3 to 5 centimeters in diameter were present on the forearms and legs. Nonulcerated skin was indurated and edematous; areas with dried, scaling surfaces were also present. There was 200 ml of clear yellow ascitic fluid in the peritoneal cavity and 20 to 30 ml in each hemithorax.

The pancreas was enlarged and was surrounded and infiltrated by a large zone of hemorrhagic necrosis. The parenchyma, where visible, appeared dark red and soft. The pancreatic duct was dilated but contained no stones. The extrahepatic biliary tree was normal.

Almost all body fat showed necrosis, which was in general nonhemorrhagic. Cut section of the thick subcutaneous panniculus over the upper anterior thorax had the classical indurated marbled white opaque appearance of necrotic fat. The right kidney weighed 126 gm and the left 149 gm (the expected weights are 73 and 74 gm, respectively). The cortex on cut surface appeared pale and smooth with normal thickness but poor corticomedullary demarcation. The liver was pale and large, weighing 1,158 gm (expected weight 712 gm) and the spleen appeared atrophic, its weight 36 gm against an expected 68 gm.

Microscopic Findings

The renal process found was consistent with that of "lipoid nephrosis." The glomeruli showed minimal nonspecific glomerulitis characterized by mesangial thickening. They were normal in number and none were hyalinized. Tubules showed generalized slight luminal dilatation without specific epithelial changes. Occasional hemorrhagic microabscesses were present and they contained fungi with morphologic characteristics consistent with cryptococcus neoformans and candida albicans.

There was hemorrhagic pancreatitis with occasional inflammatory infiltrate in the edematous and hemorrhagic septa. Fat necrosis without calcification was prominent in peripancreatic fat deposits and the islets appeared normal. There was no vasculitis (Figure 2). The liver showed fatty metamorphosis while the appearance of the adrenal cortex was that of stress response with pseudotubular degeneration.

The fat necrosis found was subacute, without calcification, cyst formation or hemorrhagic areas.

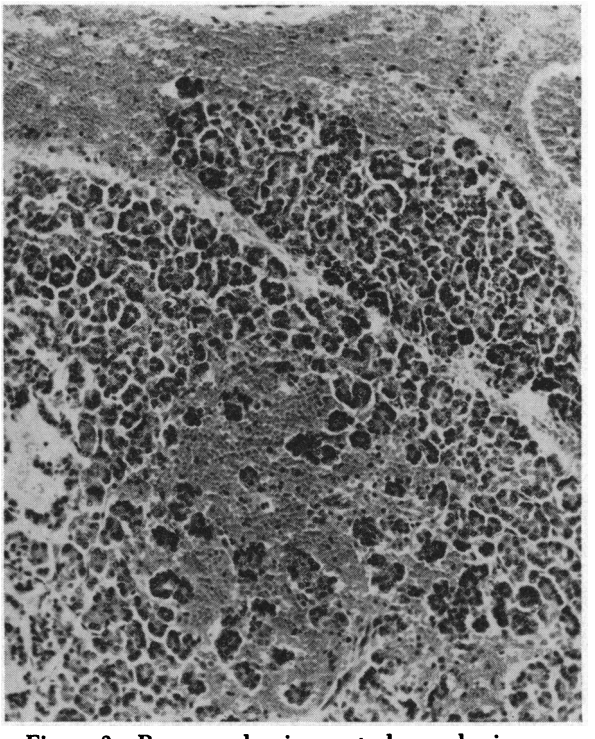

Figure 2.—Pancreas showing acute hemorrhagic necrosis of parenchyma (Hematoxylin and eosin stain, ×125).

Epidermal ulceration was demonstrated. The dermis was atrophic, with loss of adnexa. Necrotic subcutaneous fat with neutrophilic infiltrates formed the base of the ulcers.

The subcutaneous fat showed, in addition to necrosis, infection by yeasts, morphologically consistent with candida albicans and cryptococcus neoformans (Figures 3 and 4).

Similar yeasts were seen in the small foci of renal infection, and candida albicans alone was seen in foci of enteric and colonic ulceration, as well as in myocardial abscesses. There was no evidence of meningitis. Fat necrosis was present in peritoneal fat, colonic submucosal fat and epidural fat.

Additional findings included atheromatosis of the aorta, agonal thrombosis of right and left ventricles of the heart, pulmonary edema with foci of reactionless bacterial growth, lymphoid atrophy, osteoporosis, conversion arrest of rib and vertebra, colloid depletion of the thyroid gland and hypertrophy of the left ventricle. A parathyroid gland was normal. The bone marrow revealed moderate myeloid and erythroid hypoplasia.

Postmortem cultures of heart blood yielded candida albicans. Heart blood and lung cultures grew betaenterococcus. The cryptococcus-like yeast was not isolated.

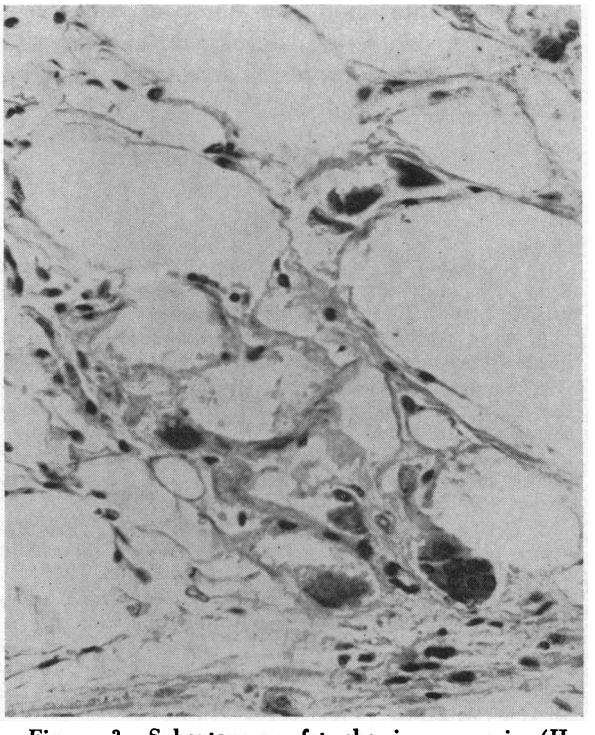

Figure 3.—Subcutaneous fat showing necrosis (Hematoxylin and eosin stain, ×325).

Discussion

Etiologic concepts and data on the incidence of "acute pancreatitis" have been confused by use of the same term for the classical clinical disease, with or without autopsy confirmation, as for incidental autopsy findings. Reported pancreatic lesions described as "acute pancreatitis" may vary from acute hemorrhage and necrosis[2] to variable foci of interstitial edema, ductular and acinar dilatation, degeneration and inspissation of secretions.[4,15] Often the findings are similar to those of "pancreatic autolysis," frequently interpreted in autopsy of adults as a meaningless phenomenon.[17,21] The significance of this appearance should not be minimized, however, because in many instances peripancreatic fat necrosis has been coexistent with it.[17,21] Variations in the microscopic appearance of "pancreatitis" may have etiologic or pathogenetic significance when the many agents or factors which have been implicated in its development are analyzed.

The incidence of pancreatitis diagnosed at autopsy is apparently reliably higher in children who were receiving steroids than in those who were not.[15] These children usually have not had classical clinical findings. Early reports described steroid-associated pancreatitis as most often mild, patchy and interstitial rather than diffuse and hemorrhagic.[4,15,17] Therefore, steroids may not be so directly related to acute hemorrhagic pancreatitis as has been implied. The majority of patients with steroid-associated acute hemorrhagic pancreatitis have been treated for "collagen diseases." Similar pancreatic involvement has also been encountered in patients receiving steroids who have chronic renal disease and hypertension. Pancreatic lesions,

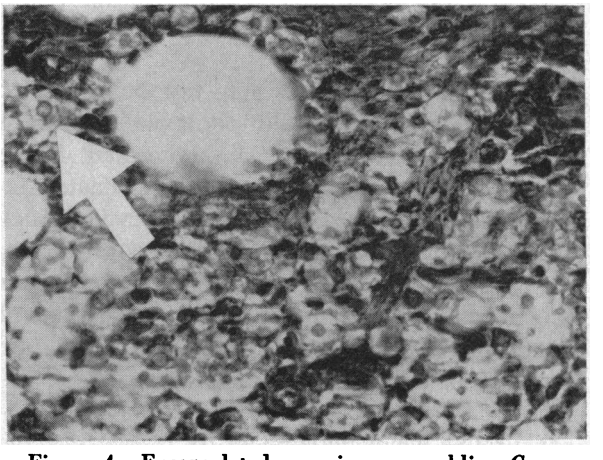

Figure 4.—Encapsulated organisms resembling *C. neoformans* in subcutaneous fat (Gridley stain, ×200).

however, occur in these patients in the absence of steroids, although with a lesser incidence.[15]

Since the pancreatitis noted in most patients with asthma or leukemia treated with steroids is not acute and hemorrhagic but patchy and milder,[15,21] vascular lesions common to both collagen disease and to chronic renal disease with hypertension may be a critical factor, resulting in progressive hemorrhagic disease.

McKay,[13] on the other hand, suggested that the common denominator in the genesis of pancreatitis may be intravascular coagulation. The effect of lipids upon platelet aggregation[7] may provide a unified concept for the diverse clinical circumstances in which hyperlipemia, vasculitis and pancreatitis coexist (for example, familial hyperlipemia, diabetes mellitus, collagen diseases and steroid-resistant nephrosis).

Recently, pancreatitis associated with immunosuppressive therapy has been reported by Tilney and coworkers,[19] who discussed the role of the drugs prescribed in conjunction with the underlying diseases, and their consequences. These investigators reported two cases in which acute hemorrhagic pancreatitis developed following renal transplantation, while the patients were receiving azathioprine (Imuran®) and corticosteroids. They postulated that patients receiving immunosuppressive therapy might fail to form antibodies to products of limited pancreatic necrosis. In the absence of these protective antibodies, subsequent necrotic foci may not be contained and thus pan-pancreatic hemorrhagic and necrotizing lesions may result.[1] Both of the patients had significant chronic and acute pancreatic vascular lesions. Despite clinical evidence compatible with "malignant hypertension," extrapancreatic vascular beds were not described and the vascular lesions were designated as "vasculitis of rejection."

Clinically, pancreatitis may not be suspected unless abdominal pain with peritoneal tenderness and elevation of serum amylase are present. In the case herein reported, extensive disseminated fat necrosis provided a diagnostic clue even though the patient at no time complained of severe abdominal pain. Both disseminated and subcutaneous fat necrosis are well recognized complications of pancreatitis and descriptions of these lesions are included in discussions of pancreatitis.* One observer proposed that fatal chronic relapsing nonsuppurative panniculitis might be, in fact, chronic pancreatitis associated with subcutaneous fat necrosis.[14] This proposal implies that pancreatitis may be relatively painless even when associated with disseminated fat necrosis. Observation of the patient in the present case lent support to this thesis. The severity of the skin lesions may be explained in part by secondary fungal infection. Candidiasis and cryptococcal infections either singly or in combination are known to occur during steroid therapy.[6,20] Candidiasis has also been reported in association with pancreatitis in patients who have not received steroids.[3,16]

*Reference Nos. 5, 8, 9, 10, 11, 18.

Summary

Disseminated fat necrosis with severe skin involvement developed in a six-year-old Negro boy with nephrosis resistant to prolonged steroid therapy who also received a 40-day course of 6-mercaptopurine. At autopsy acute hemorrhagic pancreatitis was found with subcutaneous fat necrosis and secondary fungal infection. Some of the factors implicated in acute pancreatitis, for example, steroid and immunosuppressive therapy, vasculitis, hyperlipemia and intravascular coagulation are discussed. Although the causative roles of individual factors presumed to operate at different points in the pathogenesis of pancreatitis cannot be completely established, the possibility of relatively silent pancreatitis should be borne in mind when necrotizing skin lesions develop in patients with abnormal immune processes or who are receiving immunosuppressive drugs.

GENERIC AND TRADE NAME OF DRUG

Azathioprine—*Imuran.*

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