

## EDEMA II

### CLINICAL SIGNIFICANCE

F. A. LeFEVRE, M.D., R. H. McDONALD, M.D., AND A. C. CORCORAN, M.D.

It is the purpose of this paper to outline the clinical syndromes in which edema significantly appears, to discuss their differentiation, and to comment on the changes to which edema itself may give rise. The frequency with which edema occurs indicates the variety of its origins. Its physiologic bases have been reviewed in a former paper.<sup>1</sup>

Conditions in which edema commonly appears are summarized in Table 1. Although clinical edema usually involves more than one physiologic mechanism, it is not difficult to determine the predominant disturbance. Table 2 illustrates the physiologic mechanisms of clinical edema.

Physiologically, edema is an excessive accumulation of interstitial fluid. Clinically, it may be latent or manifest, and, by its nature, *localized* or *generalizing*. These terms, with the exception of *generalizing*, have been defined, and may be accepted. By *generalizing* edema is meant a condition in which edema is at first local in its appearance, but in which, as the process extends, edema will become general, causing anasarca. The degree of edema in any area is limited by tissue tension and the sites of its first appearance and later spread are partly determined by gravity.

#### CARDIAC EDEMA

Generalizing edema is an early manifestation of cardiac failure. It is usually considered to be evidence of inadequacy of the right ventricular musculature (back pressure theory). Peripheral edema may be accompanied by pulmonary edema in cases where there is simultaneous left ventricular failure. Actually, the genesis of cardiac edema may depend more on sodium retention<sup>2,3,4</sup> due to "forward cardiac failure" and renal constriction than on venous back pressure alone. The onset of cardiac edema is preceded by increases in blood and interstitial fluid volume. At times it is latent, and gravity causes it to become manifest earlier in the ambulatory than in the bedridden patient. The onset of latent edema may be predicted by careful daily weighing.

Cardiac edema usually appears first above the external malleolus and over the inner portion of the lower end of the tibia where the underlying bone renders pitting easy to detect. It tends to disappear with recumbency and is accentuated by any cardiac pressure, as from a garter. It is usually symmetrical and bilateral unless local disturbances, such as unilateral varicosities, complicate it.

## EDEMA II

TABLE 1  
SYNDROMES IN WHICH EDEMA APPEARS

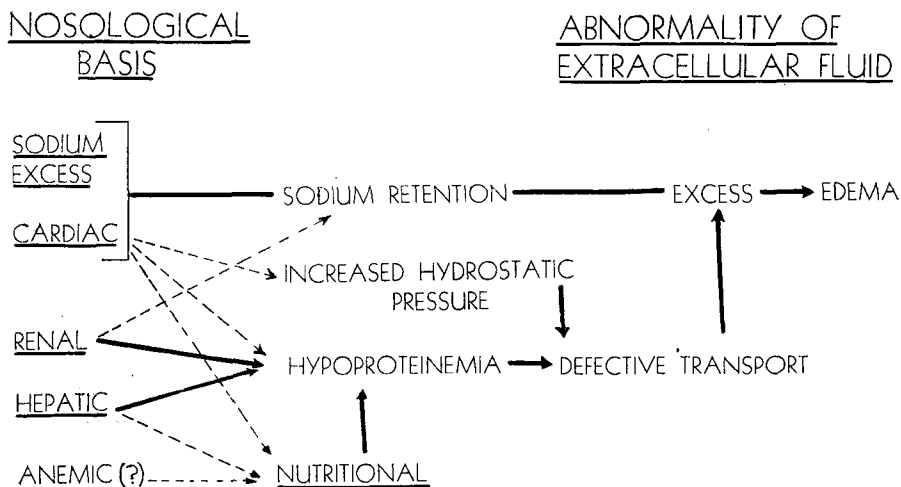
| Types                            | Examples                                                                                                                                                                                                    |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>GENERALIZING EDEMAS</b>       |                                                                                                                                                                                                             |
| CARDIAC.....                     | Congestive cardiac failure.                                                                                                                                                                                 |
| NEPHRITIC.....                   | Acute and chronic glomerulonephritis and pyelonephritis; preeclampsia and eclampsia; toxic nephroses (CCl <sub>4</sub> , Hg, etc.).                                                                         |
| HEPATIC.....                     | Toxic and infectious hepatic disease; cirrhosis.                                                                                                                                                            |
| NUTRITIONAL.....                 | Deficiencies of protein and vitamin.                                                                                                                                                                        |
| ENDOCRINE.....                   | Premenstrual edema; desoxycorticosterone acetate overdose.                                                                                                                                                  |
| SODIUM EXCESS.....<br>(Absolute) | Excess sodium intake. Relative sodium excess is most common coincident factor in other generalizing edemas.                                                                                                 |
| <b>LOCALIZED EDEMAS</b>          |                                                                                                                                                                                                             |
| <b>VASCULAR</b>                  |                                                                                                                                                                                                             |
| Lymphatic.....<br>(Lymphedema)   | Congenital lymphangitis; Milroy's disease; recurrent lymphangitis; filariasis.                                                                                                                              |
| Venous.....                      | Varicose veins; thrombophlebitis (acute and chronic); phlebothrombosis; phlebitis secondary to disease (polycythemia, brucellosis, typhoid, etc.).                                                          |
| Arterial.....                    | Thrombo-angiitis obliterans; Raynaud's disease.                                                                                                                                                             |
| <b>EXTRA-VASCULAR</b>            |                                                                                                                                                                                                             |
| Mechanical.....                  | Obstruction to lymphatic and venous flow; compression of main lymphatic and venous trunks by obesity, neoplasm, scars, fibrosis following radiation; direct invasion of nodes or lymph vessels by neoplasm. |
|                                  | Pelvic or abdominal tumors (edema of lower extremities); mediastinal and axillary tumors (edema of upper extremities); hernia.                                                                              |
| Traumatic.....                   | Local drug injection (venous sclerosis); local injury (stretching of extremity); fracture; vibration; foot strain; exposure to temperature changes (frostbite, burns, heat, immersion foot).                |
| <b>TOXIC</b>                     |                                                                                                                                                                                                             |
| Inflammatory and Allergic.....   | Drugs (heavy metals, thiouracil); urticaria (specific or non-specific); trichinosis; sunburn; toxic erythema.                                                                                               |
| <b>PSEUDO-EDEMAS</b>             |                                                                                                                                                                                                             |
| <b>LIPDEMA</b>                   |                                                                                                                                                                                                             |
| <b>MYXEDEMA</b>                  |                                                                                                                                                                                                             |

In bedridden patients cardiac edema tends to appear first in the sacral area and will shift its location with changes in sleeping positions. In orthopneic patients who sit forward in the chair it may be most marked in the anterior abdominal wall, scrotum, or vulva.

In contrast to hypoproteinemic edema, cardiac edema commonly and early involves serous cavities. The first cavity to be affected is often the right pleural space, possibly because of mechanical pressure from the dilated heart on the azygos vein. Severe cardiac edema involves all the subcutaneous tissue and serous cavities, the face being spared because of the coincident orthopneic position. Accumulations of serous fluids in the pleural spaces reduce lung volume and thus increase the respiratory embarrassment of cardiac failure. Postmortem studies reveal intense congestion and edema of all organs including the brain and leptomeninges. Cardiac edema pits readily and pitting disappears sooner than in the edema of glomerulonephritis, probably because venous engorgement and dilatation, as well as fluid excess, increase tissue volume. The edematous skin lacks the white appearance of renal edema, and there may be some associated cyanosis.

In long standing cardiac edema, thickening and hardening of the true skin may occur as a result of secondary inflammatory reactions and loss of elasticity. Such skin is thick and brawny, pits with difficulty and is somewhat reddened and irregularly pigmented. When pressure overcomes the limitation of the skin's resistance, actual rupture with

TABLE 2



Solid arrows indicate primary, and dash arrows indicate secondary pathways of edema formation.

drainage may occur. This complication, however, is less common in recent years with better management of these patients and the use of the newer diuretics.

### NEPHRITIC EDEMA

Nephritic edema has important differences in mechanism and distribution as it appears in acute hemorrhagic glomerulonephritis, acute nephritis of insidious onset, or the nephrotic stage of glomerulonephritis:

The edema of acute hemorrhagic glomerulonephritis is less influenced by gravity than cardiac edema and manifests itself as a painless, pale, swelling, which pits with some difficulty. It is first noticed in the loose tissue of the orbit, in the eyelid, about the face, hands, scrotum, or vulva. It seems to originate largely from increased capillary permeability resulting from generalized vascular damage of the same type causing glomerular capillary damage. Nephritic edema is therefore in a sense inflammatory. The high protein content of the edema fluid tends to prevent its rapid absorption through the capillaries, and at the same time, salt retention, due to the renal lesion increases the tendency to fluid retention. Hypoproteinemic edema later supervenes.

Although acute nephritic edema may become generalized, it rarely assumes the degree seen with congestive failure. At times localized areas of edema occur which become important because of location. For instance, edema of the glottis may cause choking or asphyxia. Foci of edema in the cerebral cortex may account for convulsive seizures common in acute nephritis in children. The edema of the acute nephritic attack lasts only several days, or at the most a few weeks, and subsides without secondary complications. Cardiac failure is not uncommon during an acute nephritis and its appearance adds another mechanism to the production of nephritic edema.

Less commonly, nephritic edema first appears as a soft, pitting swelling of the ankles, shins, thighs, scrotum or vulva. In this form the onset of the disease is insidious rather than stormy. The edema is primarily hypoproteinemic and renal with sodium retention. The prognosis of the disease in this form is highly unfavorable.

The nephrotic phase of chronic glomerulonephritis, which at times is simulated by pyelonephritis, has a generalized edema as a persistent or recurrent feature. Certain cases, however, run their course without an obvious nephrotic phase, but rather with azotemia and renal insufficiency as an early, predominant feature. An interesting clinical observation is that because of increased sodium loss and because the plasma protein level rises, the edema of chronic nephritis lessens when uremia impends.

Hypoproteinemia is the major etiologic factor in chronic renal edema. The edema presents as a generalized, painless, pale swelling which may vary considerably in degree from day to day or week to week. At times massive renal edemas occur which may persist steadily for months with only minor variations in degree. In such cases the serous cavities are sometimes involved. Such massive edema predisposes to erysipeloid infections which may subside, leaving the skin thickened and reddened. Separation of the cutaneous elastic fibers results in the appearance of striae. As in cardiac anasarca, actual breaks in the skin surface occur with drainage and secondary infection. Terminally, with the onset of uremia, collections of fluid may follow the development of a sterile fibrinous pericarditis or pleurisy.

As in acute nephritis, sodium retention due to renal damage contributes to the edema. This contribution rather than changes of plasma protein might account for the unexplained, rapid variations in body weight and manifest edema. Cardiac failure also complicates the pattern.

Nephrosis is characterized by massive edema, hypoproteinemia, lipemia, and albuminuria. It is differentiated from the nephrotic stage of chronic glomerulonephritis by the absence of signs of renal irritation (red and white blood cells in the urinary sediment), and by its favorable course. The diagnosis of nephrosis should be made with greatest of caution in adults. This rare disease is somewhat more common in children. As in other edemas the skin is subject to erysipeloid infections. The course of nephrosis is sometimes complicated by abdominal pain, vomiting, and prostration which have been shown to be associated with the disappearance of amino acids from the blood.<sup>5,6</sup> These bouts which are frequently mistaken for attacks of pneumococcal peritonitis may be instantly cut short by intravenous administration of amino acid mixtures.

The third trimester of pregnancy is normally associated with an increase in plasma and interstitial fluid volumes which predispose to edema. Because of the weight of the gravid uterus, this edema is usually localized and manifest at the ankles. Eclampsyogenic toxemias of pregnancy (pre-eclampsia and eclampsia) are characterized by generalizing edema which is especially manifest in the face, conjunctiva and hands. This edema and the coincident changes of renal function,<sup>7</sup> closely resemble that of acute glomerulonephritis. Because toxemia is often associated with prior malnutrition, however, hypoproteinemia is often a complicating factor.

#### HEPATIC EDEMA

Hepatogenous edema may be localized or generalizing. Ascites in the course of hepatic cirrhosis is a form of localized edema with peri-

toneal transudation dependent upon increased portal venous pressure. Generalized edema of hepatic origin may appear in any form of hepatic disease which is sufficiently extensive to impair the liver's ability to form new protein, and more particularly, serum albumin. It is, therefore, a form of hypoproteinemic edema which occurs as a complication of toxic and infectious hepatic disease and in hepatic cirrhosis. In none of these diseases is it commonly so extensive as to constitute a hazard in its own right.

#### NUTRITIONAL EDEMA

Edema may result from protein starvation or from protein lack with inadequate vitamin intake. Edema rarely results from vitamin deficiency alone.

Dietary protein deficiency can cause a sufficient decrease of serum protein to produce edema of a generalizing type. Such a deficiency may be absolute as in famine edema, or relative and due to increased metabolic demand (hyperthyroidism) or uncorrected protein loss (proteinuria, burns, severe eczema). Failure of gastrointestinal absorption, the result of local disease (gastro-colic fistula), or lack of utilization in the manufacturing process in the liver, may produce the same result. Protein deficiency is accentuated when the diet is low in calories as well as in proteins, because valuable stores of protein must then be burned for energy production. The failure of protein anabolism which characterizes states of damage or disease predisposes to hypoproteinemia and is only partially reversed by ingestion of large amounts of protein. One of the recently recognized complications of nutritional hypoproteinemia and edema is the tendency to disruption of wounds, particularly those of the abdominal wall.

Thiamine insufficiency may cause a mild edema of legs and ankles in association with the neuritic pain, weakness, and paresthesia due to the characteristic neurologic lesions. Gross edema appears rapidly in so-called wet beri-beri due to thiamine deficiency. The clinical picture is similar to that of cardiac decompensation from other causes. Probably the cardiac effect of thiamine deficiency is increased by antecedent cardiac damage. Diagnosis is made by therapeutic test with large doses of thiamine and other B vitamins. The heart is enlarged, particularly to the right. The electrocardiogram shows low voltage in the limb leads, T wave inversion, S-T depression and sinus bradycardia. Uncomplicated cases of wet beri-beri occur in the Orient. In this country, this form of edema is most often seen in chronic alcoholics whose disease is complicated by dietary insufficiency and gastrointestinal defect, and, in whom hepatic damage adds to the protein depletion.

## EDEMA OF ENDOCRINE ORIGIN

A more or less generalized edema may be seen as an accompaniment of certain glandular dysfunctions. Premenstrual edema is regarded as due to renal retention of sodium under the influence of inadequately metabolized ovarian steroids.

Injection of desoxycorticosterone may result in generalized edema due to excessive retention of sodium ion. This reaction is seen in the treatment of Addison's disease or may be produced in normal individuals. It is relieved by administration of potassium, sodium restriction and water or ammonium chloride diuresis.

Certain hypothalamic states are associated with undue retention of fluid in the body which may be relieved by the use of benzedrine sulphate. It is possible that these states result from a disturbance of the water-regulating hormone of the posterior pituitary. Some edema may be found in the late stages of parathyroid disease with nephrolithiasis as the result of renal damage. Edema has also been noted to follow the administration of insulin to uncontrolled severe diabetics. This edema may be an expression of an insulin-induced water imbalance. Locally, it is occasionally seen in swelling of the lens, with temporary loss of sharp vision.

## SODIUM EXCESS

Intake of sodium in excess of that which can be excreted by normal kidneys is uncommon and is usually seen only in patients given infusions of physiologic saline in large amounts causing an absolute sodium excess. More commonly, sodium excess is relative rather than absolute, being dependent upon the inability of functionally or structurally damaged kidneys to excrete a normal or even subnormal amount of dietary sodium.

## VASCULAR EDEMA

Physiologically, edema of local origin is due to an abnormality in the movement of interstitial fluid which, while it causes local excess, cannot of its nature give rise to a great absolute increase in body fluid as a whole. Movement of interstitial fluid depends on the normal transport of blood and lymph. Local edema is therefore either blood-vascular or lymph-vascular in origin. In each category it is primary and the result of vascular disease alone, or secondary and due to extravascular causes. Primary blood-vascular edema is arterial or venous, the arterial forms being rare and probably not of themselves due to arterial activity.

Thus, edema in thrombo-angiitis obliterans is more commonly due to the associated thrombophlebitis than to arterial changes as such. The edema of Raynaud's disease is probably the result of local in-

flammatory change consequent on arterial spasm and tissue necrosis, and not the effect of arterial constriction alone.

Lymphedema is chronic in nature and commonly involves the lower extremities. In a small group of cases it is congenital and present at birth, or in a type known as lymphedema praecox, it appears at puberty. Milroy's disease also belongs to this group and is sometimes known as hereditary tropho-edema or lymphedema of a familial type. In contrast is the lymphedema resulting from recurrent lymphangitis which in the tropics may be caused specifically by filariasis.

Generally, lymphedema is gradual in onset. It may be unilateral or bilateral and is frequently not associated with any localized pain. Edema of this type pits easily and, in early stages, disappears promptly when the limb is elevated. At a late stage pitting becomes difficult due to infection and fibrosis. In the later stages of lymphedema the subcutaneous tissues become thick, hard, and folded, and ulceration may result with secondary infection. When this picture occurs, the name, elephantiasis, is frequently applied.

In contrast to lymphatic edema there are those edemas due primarily to involvement of the veins. Simple varicose veins are a common cause of edema of the lower extremities. The varices may or may not be associated with secondary thrombophlebitis. When phlebitis occurs, the edema is increased.

In the case of simple varices the edema is gradual in onset. The large superficial veins are readily detectable, but extent of visible varicosities is not an exact indication of the degree of venous incompetence. Color changes are marked, there being a dark rubor which approaches a cyanotic appearance. No unusual temperature changes are noted and the edema improves when the limbs are elevated. This type of edema is more severe at the end of a day.

Edema resulting from acute or chronic thrombophlebitis of the superficial or deep (phlebothrombosis) veins may occur in the absence of varicose veins, and usually with a history of acute onset, localized tenderness, redness, swelling, and frequently, with chill and fever. If the extent of the venous occlusion is not too great, no edema may develop. If several channels of return flow are involved, edema occurs when the patient stands for long periods. There is more discomfort and considerable fatigue of the leg muscles associated with this form of edema than with others. In later stages the skin becomes thickened and has a bright reddish, shiny appearance. Ulceration is common on the inner surface of the ankle. It is well to remember that thrombophlebitis may be secondary to several diseases including polycythemia, brucellosis, and typhoid fever.



## EXTRA VASCULAR EDEMA

There are several important extra-vascular conditions resulting in secondary vascular disturbances which give rise to edema, particularly of the lower extremities. In the mechanical group are included those which interfere by pressure with lymphatic and venous return. Compression of the main lymphatic or venous trunks by fat tissue, neoplasm, postoperative scars, postradiation, fibrosis, direct invasion of the lymph nodes and vessels by neoplasm or surgical removal of these, may result in edema. Pelvic or abdominal tumors may thus cause edema of the lower extremities, and axillary or mediastinal tumors may similarly affect the arms. These masses are usually detectable by physical examination.

There are several important traumatic states which give rise to local edema. Edema of the hands particularly, is occasionally noted following intravenous injection of drugs which cause thrombosis. Traumatic phlebitis may occur following local injury. Repeated, severe stretching of the arms is an occasional cause. Instances of this form of traumatic thrombophlebitis have been observed repeatedly in window washers. The "shelter edema" of the London Blitz resulted from compression of popliteal veins after long nights spent in deck chairs.

Local edema may also follow injury, particularly fracture. It may occur when fracture is not apparent, as from fracture of the small bones of the hands and feet. Chronic foot strain associated with mechanical foot defects is a common cause of mild localized edema. The immobilization which follows hemiplegia reduces blood and lymph flow and leads to minor degrees of local edema.

Edemas following frost bite, burns, and immersion foot are actually vascular and, in a degree, inflammatory. They are essentially secondary, however, to changes in temperature and environment. Diagnosis is simple because of the history of exposure.

A minor, but because of its frequency, differentially important form of edema, is that observed in women whose ankles and feet swell in summer. Such patients are usually those with well marked malleolar fat pads or a stocking type of subcutaneous fat deposit. The basis for this edema rises in vasodilation and increased transudation into an area of relatively low tissue tension, combined with high local venous pressure. Similar increased vascular permeability and blood flow are the probable causes of "heat edema" seen in the tropics or during heat waves in temperate climates. To a degree, heat edema is generalizing, for heat also tends to increase blood and interstitial fluid volume.

Certain chemical substances, particularly arsenicals, cause edema apparently as a result of capillary damage apart from or in association

with renal and hepatic lesion. Toxemia from certain infections, for example diphtheria, may act in a similar fashion.

A toxic type of cutaneous edema is that experimentally produced by the injection of hematoporphyrin in animals. The pigment sensitizes the skin so that subsequent exposure to light produces marked edematous swelling. Occasional instances have been noted in humans with congenital porphyria. Since these forms result from generalized changes they might be thought of as generalizing edemas. They merge imperceptibly, however, into the group of localized edemas caused by allergic sensitizations of all types, whose varied expressions and causes range from horse serum to hair dye, and from house cats to focal infections and rheumatic diatheses.

In the inflammatory group local edemas secondary to arthritis and local cellulitis are included. In the case of arthritis the swelling is localized to the affected joint areas, and signs of local tenderness, inflammation and restricted motion are present. Local edema may form distal to the joint, because of increased venous pressure from the site of arthritic inflammation. Trichinosis with its characteristic facial edema and eosinophilia is a member of this group.

Localized cellulitis secondary to trauma and infection may occur with resulting local edema. The area involved is centrally swollen, red, tender, and peripherally diffusely edematous. The onset is sudden with fever and leukocytosis.

#### PSEUDO-EDEMAS

So called lipedema, an abnormal local deposit of fat, frequently occurring about the ankles and the calves, may be confused with actual edema. It is nonpitting and nonpainful. During the summer especially it may cause true edema as noted above.

Myxedema of course is not a true edema, since the subcutaneous thickening is due to a myxomatous tissue deposit and not to increased intercellular fluid. Sluggish peripheral circulation, however, may result in an actual edema of the skin and subcutaneous tissue. Similarly, scleroderma and its congener, dermatomyositis, may be mistaken for edema. This confusion is not likely in the case of pseudohypertrophic muscular dystrophy.

#### REFERENCES

1. Coreoran, A. C.: Edema I. *Cleveland Clin. Quart.* **12**:117 (October) 1945.
2. Schroeder, H. A.: Studies on congestive heart failure; importance of restriction of salt as compared to water. *Am. Heart J.* **22**:141-153 (Aug.) 1941.
3. Fletcher, P. H., and Schroeder, H. A.: Studies on congestive heart failure; impaired renal excretion of sodium chloride. *Am. J. M. Sc.* **204**:52-62 (July) 1942.

4. Warren, J. V., and Stead, E. A., Jr.: Fluid dynamics in chronic congestive heart failure. *Arch. Int. Med.* **73**:138-147 (Feb.) 1944.
5. Farr, L. E., and MacFadyen, D. A.: Hypoaminoacidemia in children with nephrotic crises. *Am. J. Dis. Child.* **59**:782-792 (April) 1940.
6. Farr, L. E., Emerson, K., Jr., and Fitcher, P. H.: Comparative nutritive efficiency of intravenous amino acids and dietary protein in children with nephrotic syndrome. *J. Pediat.* **17**:595-614 (Nov.) 1940.
7. Corcoran, A. C., and Page, I. H.: Renal function in late toxemia of pregnancy. *Am. J. M. Sc.* **201**:385-396 (March) 1941.

## VON GIERKE'S GLYCOGEN DISEASE

### *Report of Two Cases*

R. W. SCHNEIDER, M.D.

The purpose of this report is to present two cases of von Gierke's glycogen disease, to discuss its clinical characteristics, to review the present concept of the disease, and to digress somewhat on the mechanism of acidosis, particularly in children.

Von Gierke's glycogen disease is apparently limited to infancy and childhood. It is chronic, often with a familial tendency, and is characterized by an excessive accumulation of glycogen in various organs of the body, especially the liver, with subsequent enlargement of the affected organs. The stored glycogen, which cannot be mobilized,<sup>1</sup> seems to have normal chemical and physical properties and can be hydrolyzed by normal liver tissue. The liver may extend to the iliac crest, yet there is neither splenomegaly, ascites, nor jaundice. Appreciable impairment in liver function is not common. The fasting blood sugar is consistently low, usually without symptoms of hypoglycemia. Fasting acetonuria, lipemia, and hypercholesterolemia are not uncommon. Epinephrine may increase acetonuria but does not cause as great a rise in blood sugar levels as would occur normally.

The etiology and pathogenesis of the disease are not clear. It has been postulated that the fetal type of glycogen metabolism may persist into postnatal life,<sup>2</sup> since fetal glycogen does not disappear rapidly by spontaneous glycogenolysis and cannot be readily mobilized by the administration of epinephrine.<sup>3</sup> It has been suggested that the presence of diastatic ferment in the liver is necessary before epinephrine can release glucose from hepatic glycogen stores and that this enzyme is diminished or absent in this disease.<sup>4</sup> The chief organs affected are the liver, heart, kidneys, and brain, apparently in that sequence. Death