CURRENT OPINION

Re-evaluation

Role of malnutrition, hepatic dysfunction, and gastrointestinal bacteria in the pathogenesis of acute toxemia of pregnancy

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IN THE southern United States acute toxemia of pregnancy occurs in its highest frequency among women in the lowest socioeconomic strata. The idea that malnutrition plays some role in the pathogenesis of acute toxemia has been advanced by Strauss,[1] Burke,[2] and others. However, there has been no general acceptance of this idea because no one has demonstrated *how* malnutrition can produce the signs, symptoms, and clinical course of this disease. Further complicating the problem is the common clinical fact that well-nourished women may develop edema and mild hypertension without proteinuria near term. It is quite possible that this "mild toxemia" which responds readily to diuretics and salt restriction is not pre-eclampsia at all; these women may never develop the severe fulminating disease so commonly seen in the poor, nonclinic, malnourished woman. Severe toxemia requires hospitalization and is often refractory to all current therapies except termination of pregnancy.

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Malnutrition can lead to hepatic dysfunction. There is evidence that the liver's detoxication mechanisms are impaired in acute toxemia, and a mechanism by which protein malnutrition can lead to such impairment has been discussed.[3] Since the gastrointestinal bacteria produce within the lumen of the lower bowel certain aromatic compounds which are detoxified by the liver, it is reasonable to suspect that these bacteria may play some role in the pathogenesis of acute toxemia.

Eclampsia was for a long time considered to be caused by the absorption of toxic substances from the bowel, and many vigorous efforts have been made to purge and lavage away the noxious agents. The name "toxemia" bears witness to these simple, old, and apparently foolish notions. Theobold[4] of England, writing about the pathogenesis of toxemia in 1956, stated with final authority: "The auto-intoxication hypothesis is dead. . . ." This idea has been discarded without an adequate test; an adequate test is now possible because of the recent discovery of potent antimicrobics which can effectively suppress the gastrointestinal bacterial flora.

Ammonia and certain aromatic and nitrogenous compounds such as indole, phenols,

cresols, tyramine, etc., are produced by gastrointestinal bacteria as they metabolize amino acids in the lumen of the lower bowel. Some of these compounds are potentially toxic and are absorbed and carried to the liver via the portal vein. If the liver is healthy, these substances are readily detoxified by conjugation with glucuronic acid and sulfate, and the amines are oxidized by amine oxidases. These compounds are thought to play a role in the pathogenesis of hepatic coma.[5] The value of intestinal antisepsis in the management of hepatic coma, impending coma, and portal systemic shunts has been well established since 1955.[6] We have thus a precedent from our colleagues in internal medicine; if the liver begins to fail in its function of detoxication, the bowel *can* become the source of toxic compounds capable of causing damage to the body. The reduction in smooth muscle tone and the crowding of the gastrointestinal tract by the expanding uterus produce a unique situation in pregnancy in which constipation is notorious and the opportunities enhanced for absorption of these potentially toxic compounds.

The following compounds, all arising in the gastrointestinal tract and all detoxified primarily in the liver, have been reported to be present in abnormal quantities in the serum or urine of patients with toxemia: tyramine,[7] indican,[8] indole,[9] and serotonin. The Krupps[10] of Tulane, in 1960, concluded from their studies: "There is no reason to postulate increased serotonin production in the eclamptogenic toxemias, but rather it would seem more likely that in some instances its detoxication is delayed or inhibited." Serotonin is detoxified primarily in the liver by an amine oxidase. It is not possible to implicate any one of these substances as producing signs or symptoms of toxemia, but the fact that they appear in the serum or urine in abnormal amounts is further evidence that the hepatic detoxication systems of toxemic patients are overloaded or impaired.

The symptoms of severe toxemia suggest liver disease: anorexia, nausea, vomiting, malaise, and epigastric pain. Other biochemical evidence of liver dysfunction in acute toxemia includes elevation of serum alkaline phosphatase activity (values of 8 to 16 Bodansky units are common in severe toxemia), increased plasma fibrinogen, hypoalbuminemia, and evidence of glycogen depletion with ketones in the urine and metabolic acidosis.

In the recent literature there is accumulating evidence that the normal maternal organism may have some impairment in conjugation of steroids with glucuronic acid. Jailer[11] and Migeon[12] have investigated this problem in relation to adrenal cortical steroid metabolism in normal pregnancy and suggest that a normal pregnant woman at term has some impairment of this mechanism. Venning[13] in 1954 reported finding a reduction in urinary excretion of corticosteroids conjugated with glucuronic acid in toxemic women as compared to normal women. Frantz[14] has reported finding increased amounts of 6-OH-cortisol, the principal *un*conjugated corticosteroid, in urine of toxemic women, and suggests that there may be some alteration in the usual conjugation mechanisms in toxemia. The urinary excretion of conjugated pregnanediol is diminished in toxemia when compared with normal pregnancy.[15] It is likely that this is related to impaired hepatic conjugation of pregnanediol and not to decreased production of progesterone by the placenta as has been so long believed. Eton and Short[16] have found normal plasma levels of progesterone in toxemia and elevated levels in twin and diabetic pregnancies. Several investigators have reported finding a reduction in urinary excretion of aldosterone in toxemia when compared with normal pregnancy.[17] The urinary excretion of estrogens has likewise been found to be reduced.[18] All of these endocrine studies in toxemia can be explained by impaired hepatic conjugation and excretion of these steroids. As pregnancy advances toward term the placental production of steroids, estrogens and progesterone, increases; this puts an extra load on the hepatic detoxication enzyme systems.

Several of the aromatic compounds produced by gastrointestinal bacteria (indole, phenols, and cresols) are conjugated with glucuronic acid and sulfate in the liver.

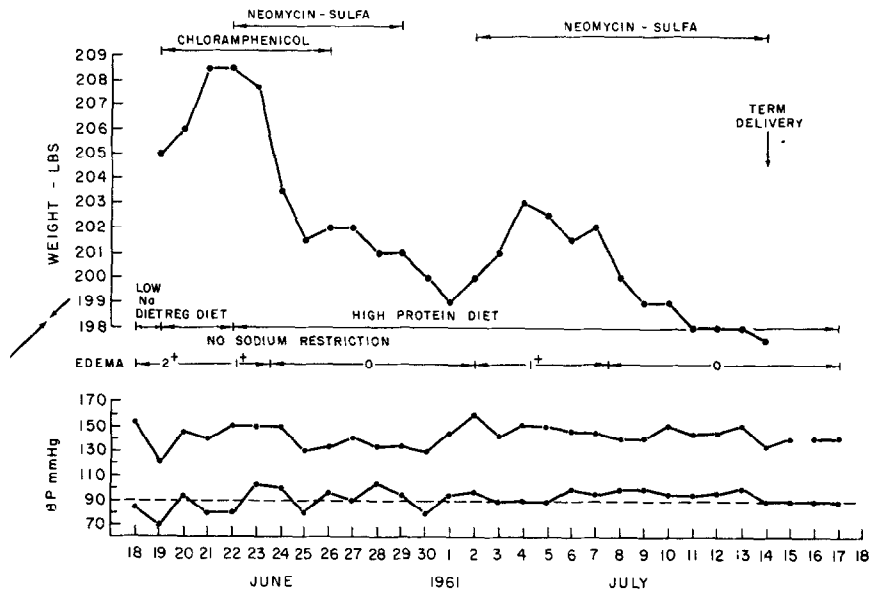

Fig. 1. Twenty-four-year-old primigravida with history of poor diet, exogenous obesity, chronic hypertension with superimposed acute toxemia. Patient received no diuretics and was fully ambulatory. (Note reaccumulation of edema when bowel preparation was discontinued.)

These bacterial compounds thus utilize the same substrates for conjugation as do the steroids, and they can interfere with steroid detoxication either by competitive inhibition or by causing direct damage to liver cells, resulting in hemorrhagic necrosis. It seems reasonable to attempt to reduce the load on these hepatic detoxication enzyme systems by reducing the gastrointestinal bacterial flora with antibiotics.

To date 16 patients in the third trimester with mild and moderately severe pre-eclampsia have been treated on a regimen aimed at improving their protein reserves and reducing the bacterial flora of their gastrointestinal tracts. They were treated essentially as if they had liver disease. They were kept ambulatory and had no sodium restriction. They were given a high-protein diet of about 2,200 calories with 120 grams of protein. They received neomycin and phthalylsulfathiazole as described by Poth for a regular surgical bowel preparation.[19] The results have been encouraging and will be reported in detail elsewhere. Figs. 1, 2, and 3 show typical courses in the hospital before delivery. Ten patients had marked reduction of edema

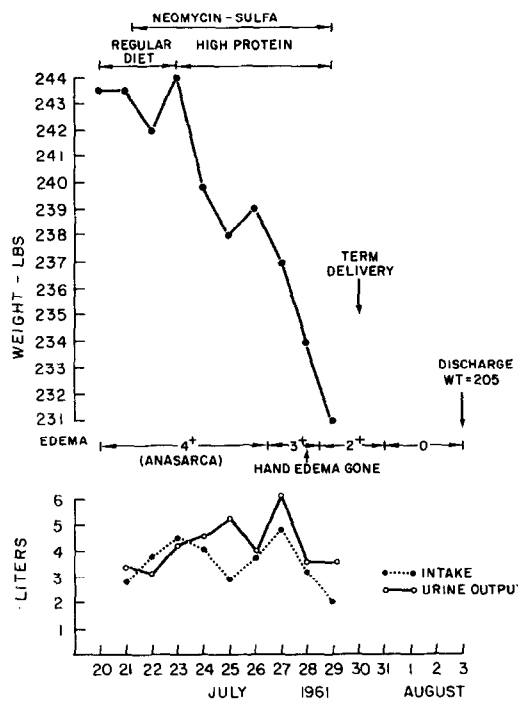

Fig. 2. Markedly obese 24-year-old multipara with history of poor diet and with acute toxemia superimposed on chronic hypertension. She lost 13 pounds before delivery. She received no diuretics, no salt restriction, and was fully ambulatory after the third hospital day.

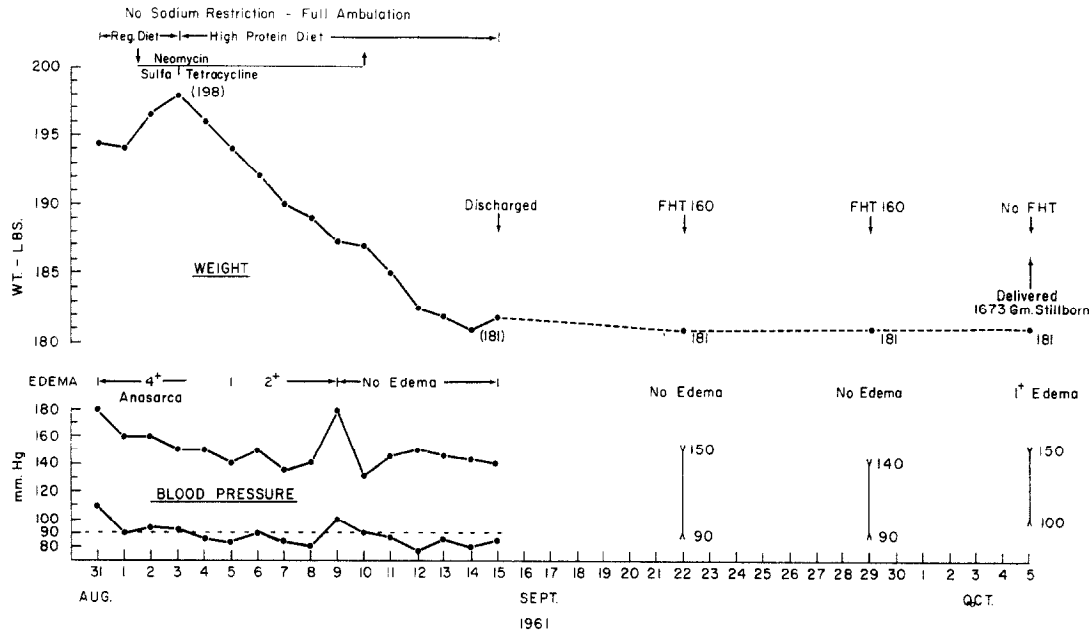

Fig. 3. Markedly obese and malnourished 29-year-old primigravida who had been on oral diuretics for one month prior to admission. Diagnoses included mild chronic hypertension with superimposed acute toxemia. She received no further diuretics, no salt restriction, and was fully ambulatory.

with weight losses ranging from 5 to 17 pounds; in several patients it was possible to demonstrate a recurrence of edema in a few days after the bowel sterilization was stopped and a disappearance of edema when it was restarted. These patients also improved symptomatically; the headaches and anorexia were relieved, and they began to feel well. Their blood pressures were lowered and remained at satisfactory levels. Five patients were delivered before adequate time had elapsed to evaluate the results, and one patient with severe toxemia, marked malnutrition, and a twin gestation failed to respond at all. It was not possible to persuade her to eat well. Three patients with toxemia were treated with the high-protein diet alone and failed to lose a significant amount of weight.

All theories of the pathogenesis of acute toxemia of pregnancy must come to grips with the clinical and socioeconomic facts that severe toxemia is a disease rooted in poverty and nourished by ignorance; it is a metabolic disorder conditioned by malnutrition in the great majority of cases, and it is a preventable disease in our present state of knowledge.

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