Clinical Hemodynamics and Pharmacodynamics of Toxemia*

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For many years toxemia has served as a wastebasket for a variety of disease states characterized by an elevated arterial pressure, edema, and albuminuria. Whereas this triad is consistent with the diagnosis of toxemia, it is not diagnostic. Besides toxemia, these abnormalities may be found in pregnant patients with hypertensive vascular disease, pyelonephritis, glomerulonephritis, or any combination of these (fig. 1). Data derived from studies performed on patients with such a variety of disease entities have obviously been confusing. It makes a lot of difference, for example, whether the subjects studied had chronic pyelonephritis or acute vasospastic toxemia. During the past 13 years, our group has attempted to cut the pie of elevated arterial pressure, albuminuria, and edema into separate and distinct diagnostic pieces. Ophthalmoscopic examination and urinalysis have been of great help in this regard (Finnerty, 1954, 1956 and 1965; Finnerty *et al.*, 1960).

Diagnosis

Toxemia was diagnosed when the ophthalmoscopic examination revealed spasm of the retinal arteries with no retinopathy, and urinalysis revealed only albuminuria (fig. 2). Hypertensive vascular disease existed when the retinal arteries were either normal or thickened and tortuous with AV nicking. When both signs of chronic vascular disease and acute vasospasm were observed with or without albuminuria, toxemia was then superimposed on hypertensive vascular disease. The finding of normal fundi and albuminuria suggested pyelonephritis. Clumps of cells in the urine and a positive colony count documented the diagnosis.

Figure 3 gives the diagnostic breakdown in 4,273 patients followed in our toxemia clinic during the past 3 years. It is interesting to note the frequency of pyelonephritis and hypertensive vascular disease, and the relative rarity of true toxemia. The recent biopsy studies of Altchek (1961) would seem to substantiate the finding that most patients originally thought to have toxemia actually have some other disease. The specific biopsy picture for toxemia has for the first time significantly clarified this wastebasket of syndromes. It would seem that toxemia is another type of glomerulonephritis. Figure 4 shows the similarity between toxemia and glomerulonephritis. Both diseases are characterized by a greater rise in the diastolic than the systolic pressure, which causes a narrow pulse pressure. The edema is particularly in the periorbital areas, hands and feet. Ophthalmoscopic examination reveals thread-

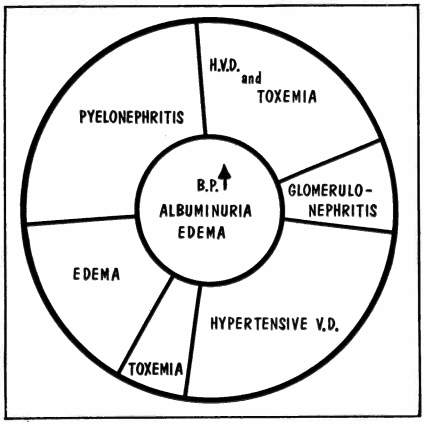

Fig.1.—Elevated blood pressure, albuminuria and edema are seen in toxemia but also in several other conditions.

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DIFFERENTIAL DIAGNOSIS OF TOXEMIA

TOXEMIA < ELEVATED B.P. / ALBUMINURIA / EDEMA

	OPHTHALMOSCOPIC EXAMINATION		URINALYSIS		
	Arterial Spasm	Retinopathy and A.V. Nicking	Alb.	W.B.C.	R.B.C.
PURE TOXEMIA	√	0	√	0	0
H.V.D.	0	√	±	0	0
H.V.D. + TOXEMIA	√	√	√	0	0
PYELONEPHRITIS	0	0	√	√	0
GLOMERULO-NEPHRITIS	√	0	√	√	√

Fig. 2—Ophthalmoscopic examination and urinalysis in the differential diagnosis of toxemia.

THE DIAGNOSIS IN 4,273 PATIENTS

1961 - 1963

PURE TOXEMIA	167	4%	6%
TOXEMIA + HYPERTENSIVE VASCULAR DISEASE	42		
TOXEMIA + PYELONEPHRITIS	67		25%
PYELONEPHRITIS	704		
PYELONEPHRITIS + HYPERTENSIVE VASC. DISEASE	287		
HYPERTENSIVE VASCULAR DISEASE	804		
GLOMERULONEPHRITIS	84		
NON-RELATED MEDICAL DISEASE (ANEMIA, HEART DISEASE, ETC.)	214		
EDEMA WITHOUT DISEASE	387		
ASYMPTOMATIC BACTERURIA	469		
NO DISEASE	944		
QUESTIONABLE DIAGNOSIS	104		
TOTAL	4,273		

Fig. 3—Diagnostic features in patients attending the toxemia clinic

like arteries and generalized wetness of the retina. Both diseases are characterized by albuminuria.

Pathologic Physiology

All the signs and symptoms of toxemia may be adequately explained by abnormal sodium retention and generalized vasoconstriction (fig. 5). The relationship between the two is unknown, but clinical observation attests that sodium retention usually precedes generalized vasoconstriction, and that prompt therapy of sodium retention usually prevents generalized vasoconstriction. The studies of Eisenberg (1959) in patients with acute nephritis, and Finnerty (1962) in patients with toxemia, show that there is an increase in plasma volume without an increase in circulating red cell mass. Following diuretic therapy the plasma volume returns to normal. This pattern of blood volume expansion, therefore, contrasts sharply with that in patients with congestive heart failure in whom there is a commensurate increase in red cell mass and plasma volume. These data suggest that an abnormality of salt and water metabolism is solely responsible for the hypervolemia of acute nephritis and toxemia.

A decrease in the amount of blood to a particular area due to increased vasoconstriction explains the remainder of the abnormality. An increase in cerebral vasoconstriction causes cerebral ischemia, leading to coma and convulsions. It is interesting in this regard to emphasize that it is cerebral ischemia, and not a rise in arterial pressure, that is the important abnormality in inducing coma and convulsions. The exact same symptoms may be caused by postural hypotension or an attack of Stokes-Adams syncope.

Evidence of both sodium retention and vasoconstriction, the two pathophysiologic abnormalities, can be visualized ophthalmoscopically. A wet, glistening appearance of the entire

SIMILARITY OF GLOMERULONEPHRITIS AND TOXEMIA

1. NARROW PULSE PRESSURE
2. LOCATION OF EDEMA
3. OPHTHALMOSCOPIC PICTURE
4. URINARY FINDINGS
5. RENAL BIOPSY

Fig. 4

retina (retinal sheen) and a decrease in the caliber of the retinal arteries characterize toxemia. The observation that the generalized sheen of toxemia is promptly decreased following diuretic therapy strongly suggests that it represents retinal edema.

Increased constriction of the peripheral vessels seems to account for the elevated arterial pressure. The increase in arterial pressure in toxemia is not associated in a change in the cardiac output. Finally, the increased vasoconstriction in the renal circulation, particularly in the afferent vessels as noted by Assali *et al.* (1953) accounts, in part at least, for the decrease in urinary output. The decrease in urinary output is part of the toxemic process and not necessarily a complication.

In summary, then, the toxemic process can be divided into two phases: the sodium retention phase, and the phase of sodium retention plus generalized vasoconstriction (fig. 6). The sodium retention phase is characterized by an increase in plasma volume which returns to normal following therapy. Prompt therapy will frequently prevent the development of the second phase.

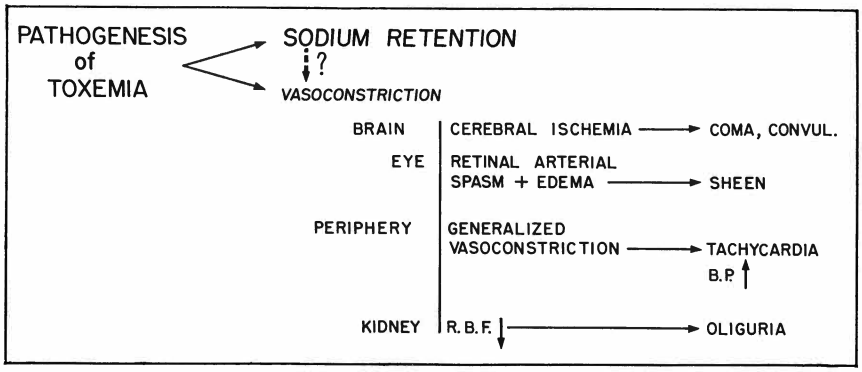

Fig. 5—Pathogenesis of toxemia

Therapy

The availability of the thiazides has completely changed the concept of the treatment of toxemia. Prior to their development, the primary aim of therapy of toxemia was directed toward the control of arterial pressure and albuminuria (manisfestations of generalized vasoconstriction). Reserpine, hydralazine, and veratrum, therefore, were used extensively in our clinic, as well as in others. If the arterial pressure could not be lowered sufficiently, additional antihypertensive agents were added.

The primary aim of therapy of toxemia, at present, is prompt control of sodium retention. The effectiveness of the thiazides in immediately controlling abnormal sodium retention, and in returning the plasma volume to normal, has frequently prevented the development of generalized vasoconstriction and thereby practically eliminated the need of antihypertensive therapy in these patients. When used alone at the first sign of excessive weight gain, the thiazides frequently reverse the toxemic process. Even more important is the observation that they can be administered continuously without the development of drug resistance, thus preventing the development of vasoconstriction. For practical purposes, the prevention of vasoconstriction is equivalent to the preventing of toxemia. In our experience, these diuretic agents have resulted in more than a 70% reduction in the number of patients with toxemia during the past two years.

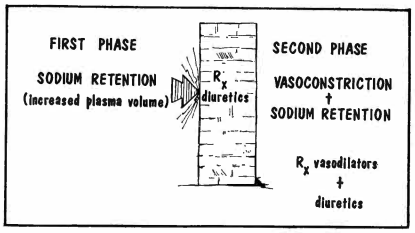

Fig. 6—Two Main phases of toxemia

If signs of vasoconstriction (retinal arterial spasm and albuminuria or either of them alone) are already present when the patient first presents herself, she probably should be hospitalized. It should be stressed that the primary aim of therapy in the hospitalized patient is preparation of the patient for delivery or Cesarean section. Whereas for the out-patient, sodium diuretics are the only agents needed, in the hospitalized patient these drugs serve only as background agents. Vasodilating agents must now also be administered.

We have recently had experience with a nondiuretic benzothiadiazine analogue whose structural formula is very similar to chlorothiazide (fig. 7). When administered by mouth it causes only a small reduction in arterial pressure, and also causes sodium retention and hyperglycemia. When administered by vein, however, it is a potent vasodilating agent. The average effective dosage is 300 mg (1 ampule) given rapidly, undiluted. To date, 69 patients with severe pre-eclampsia and 2 with eclampsia have received diazoxide with excellent results. The typical ef-

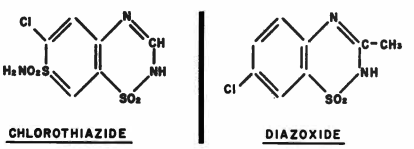

Fig. 7

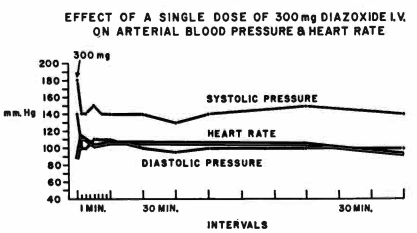

Fig. 8

fect of 300 mg of diazoxide can be seen in figure 8. A 35% average reduction in mean arterial pressure occurred during the first 2 minutes. During the next 3 to 5 minutes, the arterial pressure increased gradually, leveling off at 19% average reduction as compared with the control. No signs of postural hypotension, cerebral ischemia, or collapse were noted.

The fall in arterial pressure with diazoxide is consistently associated with an increase in cardiac output, and a decrease in total peripheral resistance. From the cardiac and cerebral hemodynamic standpoint, diazoxide resembles hydralazine since both agents cause an increase in cardiac output, heart rate, and cerebral blood flow. Actual cerebral blood flow determinations have not been performed in this laboratory, but the lack of signs of cerebral ischemia accompanying the reduction in arterial pressure, and the increase in cardiac output, strongly indicate that there is at least maintenance of the cerebral blood flow, even at the point of the greatest magnitude of hypotensive action.

Our experience thus far would indicate that diazoxide represented a real advance in the therapy of acute vasospastic hypertension.

Prevention

Experience has shown that it is easier to prevent toxemia than to treat it. Although the thiazide diuretics seem to be the ideal agents for the treatment of the sodium retention phase of toxemia, their greatest asset is that they can be given continuously without the problem of drug resistance. I feel, therefore, that the thiazides should not only be given at the first sign of sodium retention, but should be instituted from the tenth week of pregnacy in patients who are candidates for toxemia, e.g., patients with chronic hypertensive vascular disease, patients with chronic renal disease, and probably all primagravida patients. The data on more than 6,000 patients treated with thiazides has shown that the continued use of these drugs following the tenth week of pregnancy apparently is not harmful to the fetus.

References

ALTCHEK, A. Electron microscopy of renal biopsies in toxemia of pregnancy. *J. Am. Med. Assoc.* 175: 791–795, 1961.

ASSALI, N. S., S. A. KAPLAN, S. J. FOMON, AND R. A. DOUGLASS. Renal function studies in toxemia of pregnancy. *J. Clin. Invest.* 32: 44–51, 1953.

EISENBERG, S. Blood volume in patients with acute glomerulonephritis as deetermined by radioactive chromium tagged red cells. *Am. J. Med.* 27: 241–245, 1959.

FINNERTY, F. A., JR. Does vascular damage follow toxemia of pregnancy? An internist's appraisal of three hundred three patients in a toxemia clinic. *J. Am. Med. Assoc.* 154: 1075–1079, 1954.

FINNERTY, F. A., JR. The significance and treatment of blood pressure elevation associated with toxemia of pregnancy and acute nephritis. *Am. J. Cardiol.* 9: 888–892, 1962.

FINNERTY, F. A., JR. Toxemia of pregnancy as seen by an internist: An analysis of 1,081 patients. *Ann. Internal Med.* 44: 358–375, 1956.

FINNERTY, F. A., JR. Pyelonephritis masquerading as toxemia of pregnancy. *J. Am. Med. Assoc.* 161: 210–214, 1956.

FINNERTY, F. A., JR., W. D. FOOTE, G. DEC. MASSARO, J. TUCKMAN, J. H. BUCHHOLZ, AND M. J. RYAN. The significance of lateral and generalized retinal sheen. *Ann. Internal Med.* 52: 819–826, 1960.