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The Physiologic Basis of Symptoms in Eclampsia

ERNEST W. PAGE, M.D., *San Francisco*

SUMMARY

The philosophy of treatment in eclampsia cannot rest upon the principle of combatting every symptom with many therapeutic weapons until the symptom, and occasionally the patient, fades away. It should rest rather upon assisting the maternal organism to keep its own compensatory efforts within the bounds of safety, preventing damage to vital organs where possible, and removing the cause of the disease by termination of the pregnancy whenever that may be done with safety to both mother and child. Such assistance must necessarily be based upon current understanding of the disturbances which underlie each symptom.

PREECLAMPSIA and eclampsia are one and the same disease, and so far as we know, the syndrome is peculiar to human pregnancy. Because the cause is not known, there is no specific therapy, and our treatment is, therefore, symptomatic. In the past, the design of therapeutic measures has too often depended upon a trial and error method, with the acceptance or rejection of any particular drug or procedure based upon gross maternal and fetal mortality figures in various sized series of cases. Since the disease is both complex and variable in its nature, and since the death of a mother or child may or may not be related to the treatment administered, this approach has not been too fruitful. It has taught us by the sheer weight of statistics that a few procedures are bad, such as operations upon women with convulsions. It has, on the other hand, led us into a maze of rigid "systems" of therapy, no one of which is applicable to all patients.

Symptomatic therapy, by definition, must depend upon our best understanding of the disturbances which underlie the symptoms. It is toward such an understanding that the present discussion is directed, even though our existing knowledge is admittedly imperfect. A full description of the many contributions to this field cannot be undertaken here, nor can arguments for or against each viewpoint be critically considered. Scientific documentation will be by-passed, therefore, in order to present a very brief description of the most likely changes, both anatomic and functional, in the placenta, vascular system, kidneys, and brain.

CHANGES IN PLACENTAL FUNCTION

One can hardly escape the conclusion that the placenta is in some way related to the cause of preeclampsia. From an anatomic standpoint, there appears to be an increase in the various types of degenerative changes in this organ, sometimes progressing to a point where fetal life can no longer be maintained. Disturbances in the functions of placental transmission are suggested by the interruption of the normal growth rate of the fetus after the onset of toxemia, but very little is known of this. Disturbances of secretory function are reflected by the decreased urinary excretion of estrogen and progesterone end-products during preeclampsia. The best description of these endocrine changes is the

From the Division of Obstetrics and Gynecology, University of California Medical School, San Francisco.

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recent review by Smith and Smith.[23] Alterations of placental function are probably reflected likewise by the changes which preeclampsia brings about in the blood concentration of such enzymes as "Pitocinase"[15] and histaminase.[2]

It has been postulated that all of these placental changes may be secondary to disturbances in the maternal blood supply to the gravid uterus,[16, 17] and that one of the results of this relative ischemia is the liberation of thromboplastic proteins from the chorionic epithelium directly into the maternal blood stream.[21] This, in turn, might account for the shortened coagulation time of the blood in eclampsia, the deposition of fibrin in the liver, the multiple capillary thromboses in the periportal areas and the increased incidence of coagulation necrosis in the placenta. It may likewise be related to the so-called "sludging of blood" observed in preeclampsia[12] or even to the activation of the fibrinolytic enzyme system of the plasma.[22]

The hepatic changes, whatever their cause may be, often result in a stretching of the liver capsule, producing epigastric pain. Thus the occurrence of epigastric pain usually indicates that acute hepatic disease exists, and one should classify such a case as severe regardless of the blood pressure or urinary findings. We have noted the disappearance of epigastric pain during the use of heparin in such cases[13] with improvement in the toxemia in three out of four. Similar results have been reported from New York and Finland.[10] Heparin is a direct antagonist of thromboplastin, and may prove to be a valuable therapeutic measure in selected cases of preeclampsia. At present, its use must remain on a purely experimental basis; it is not recommended for general use.

CHANGES IN THE VASCULAR SYSTEM

By exclusion of all other possible factors, we arrive at the conclusion that the hypertension of eclampsia is due to a widespread arteriolar constriction.[19] This, in turn, may be due to either nervous or chemical factors, and since both are obviously operative in every individual, the problem resolves itself into the relative assessment of the role of each. If the experiments of Kellar and Sutherland[9] are valid, we may eliminate the factor of sustained increase of autonomic pressor influences as a sole cause of the arteriolar constriction and focus our attention upon biochemical changes in the blood. These changes might arise primarily from the placenta, or secondarily from some other organ such as the kidney. At present there is not sufficient evidence to ascribe the hypertension to the renal pressor system, so we are still in ignorance of the ultimate cause of the raised blood pressure.

More toxemic mothers die from the secondary effects of the hypertension than from any other single cause. These effects may be observed directly in the ocular fundi, where arteriolar constriction, edema, exudates and hemorrhages occur. These are cerebral vessels, and similar changes occur in the brain. It might be said that the disasters which follow are in a way due to the lack of time which the host has to prepare for the stress of acute and severe hypertension. Neither the blood vessels nor the heart are prepared through hypertrophy to meet this stress; so we often encounter massive cerebral hemorrhage, or acute heart failure and pulmonary edema.

Attempts to ward off such accidents include: (1) use of pharmacologic agents (e.g., the magnesium ion) which may keep the hypertension within reasonable bounds; (2) preventing, with the aid of sedatives, the superimposition of further increases of blood pressure through the nervous system, i.e., maintaining a basal condition of both physical and emotional rest; and (3) fortifying cardiac action through prophylactic digitalization. Among other secondary effects of the hypertension are irreversible vascular lesions which probably occur, particularly in the kidney, and we try to prevent this by the termination of pregnancy within a reasonable period of time when we cannot "cure" the preeclampsia.

CHANGES IN KIDNEY FUNCTION

One of the characteristic signs of preeclampsia is the occurrence of gross amounts of protein in the urine. Since from a quarter to a third of this is globulin, the term proteinuria is preferable to the term albuminuria. The source of this protein is the plasma, and the cause must be looked for in the "leaks" which occur in some or perhaps in most of the glomerular capillaries. We should not think of these "leaks" as permanent holes which can be seen microscopically, but rather as transient and intermittent changes in the size of the "pores" of the filtering membrane. These may be the intercellular interstices or the cellular membrane itself. Intermittent ischemia or transient anoxia, for example, will produce such changes, and they are quite reversible.[5] The cause of this change in toxemia is not known, but it is not due to any sustained reduction of blood supply, for the total volume of blood flowing through the kidney per unit of time is perfectly normal or even increased during toxemias.[4] It is possible, of course, that there is a direct toxic damage to the membrane by some substance originating from the placenta or decidua, because lesions of this sort may be produced by the injections of various types of tissue extracts.

A certain percentage of the protein which leaks through is reabsorbed by the renal tubules. When the amount in the glomerular filtrate exceeds the quantity which can be maximally reabsorbed, then protein appears in the bladder urine. In the process of reabsorption, the tubular cells become filled with this protein and give the appearance which has been called "albuminous degeneration."[7] Some of these cells die and are shed, but for the most part tubular function in preeclampsia remains unimpaired. The tubular lesion, in the words of Addis,[1] is the result of "a suicidal endeavor of the tubules to accomplish

an impossible task imposed by the permeability of the glomeruli."

As this protein-containing glomerular filtrate moves down the tubules, often at reduced rates of flow, it may become more acid until it reaches a pH at which some of these proteins are least soluble. They coagulate and form casts of the renal tubules, appearing as hyaline casts in the bladder urine. If the protein incorporates particulate material, we call them granular, while at other times the shed epithelial cells convert them to epithelial casts. Thus the casts go hand in hand with the proteinuria as influenced by the acidity of the urine.

At the same time that larger molecules are passing through the glomerular membrane, water is passing through more slowly. This may seem paradoxical, unless one conceives of a thickened but damaged filter. It is just such thickening of the glomerular wall that one sees in almost every case of fatal eclampsia, and we believe that this particular lesion may persist for many years after recovery from the toxemia.[18]

Most investigators who have studied the rate of glomerular filtration with inulin and such sugars agree that in preeclampsia there is often a considerable reduction. It may be reduced, for example, from 120 cc. per minute to 84 cc. per minute, or 30 per cent. Despite this reduction, the proximal tubules continue to reabsorb about 80 per cent, leaving only 24 liters per day instead of the normal 35 liters to be reabsorbed by the distal tubules. Now the distal tubules, which are not autonomous like the proximal segments, are under the control of the posterior pituitary gland, the adrenal cortex, and to some extent the estrogenic steroids. In preeclampsia, the distal tubules are "ill advised," for they may continue to reabsorb salt and water to a point where real oliguria results. It may be, as Ham and Landis have suggested,[8] that in toxemias the placenta elaborates an additional antidiuretic and achloruretic hormone, so that the usual wisdom of bodily economy is confused.

There are other alterations of tubular function in preeclampsia. Instead of rejecting the amino acid histidine, as the tubules do in normal pregnancy, there is a return to the non-pregnant status and the histidine is completely reabsorbed.[14] According to recent reports[6, 3] uric acid may be reabsorbed in greater quantities during preeclampsia. The elevated blood uric acid noted in the more severe toxemias, then, may be of renal, rather than of hepatic origin.

CHANGES IN SALT AND WATER METABOLISM

There is still much to be learned about the mechanisms which regulate the excretion of water and electrolytes. In normal pregnancy, it is believed that an increased level of steroid hormones originating from the placenta and adrenal cortex influences the distal tubules to reabsorb larger proportions of sodium and water. The diminution of plasma osmotic pressure resulting from dilution may be another factor. When preeclampsia supervenes, it would seem that the additional edema may perhaps best be attributed to the diminished glomerular filtration and further increase in salt or water reabsorption as already discussed.

Much emphasis has been placed in the past on the hypoalbuminemia which often occurs in this disease. Perhaps it is fortunate that such a reduction in the plasma albumin concentration does occur, however it may be brought about; because in the face of an impaired glomerular filter, the only means that the body has for improving or even continuing filtration are (a) a lowering of the plasma osmotic pressure and (b) an increase in the head of hydrostatic pressure, either by efferent arteriolar constriction or by systemic hypertension. We observe both a lowered serum albumin level and hypertension in the severe cases of preeclampsia. How these changes are brought about is a mystery. Nevertheless, I have enough blind faith in the wisdom of physiologic adjustments to injury to feel that these symptoms, though dangerous, serve a useful purpose. That purpose might well be the maintenance of placental transmission for survival of the fetus, or the maintenance of glomerular filtration for survival of the mother.

Since the incidental edema and oliguria may in themselves lead to a fatal outcome, it seems quite proper that we should sharply restrict the intake of the sodium ion and also displace it by the judicious use of such drugs as ammonium chloride. Hypertonic dextrose has proven its value. More recently, the employment of either plasma or serum albumin has proven beneficial even though their use, perhaps fortunately, does not restore the serum albumin to normal levels.

CHANGES IN THE BRAIN

Convulsions deserve our attention because their occurrence immediately adds to the risk of death. The combination of cerebral edema and hypertension appears to be the trigger mechanism that is responsible. We know, on the other hand, that the occurrence of convulsions does not always parallel the severity of the disease, and it must be that some women are distinctly more susceptible than others. Electroencephalographic studies of women who have had toxemias[20] suggest that those who develop convulsions during the course of preeclampsia have an underlying cerebral dysrhythmia. It is for this reason that the prophylactic use of either dilantin or mesantoin on all preeclamptic patients seems warranted. While it may be years before the value of such a procedure can be proven, these agents have proven their worth in the prevention of epileptic convulsions and seem sufficiently devoid of harm.

In similar vein, we should not, as obstetricians, overlook the possible prophylactic value of adding the amino acid methionine to the diets of our preeclamptic patients, for this agent is likewise sufficiently harmless and is known to be of value in protecting the liver against a variety of insults.

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Discussion by CHARLES E. MCLENNAN, M.D., *San Francisco*

I wish first of all to commend Dr. Page for his extremely sensible physiologic approach to the problems posed by the patient with what we choose to call preeclampsia. Too long we have been endeavoring blindly to control or correct signs and symptoms without stopping to inquire into the basic mechanisms which are responsible for these aberrations from normality. Many medical schemes or systems of treatment for preeclampsia and eclampsia have come and gone with the years, but none has done much toward solving the underlying problem because these schemes have concerned themselves solely with reduction of the level of arterial pressure and/or the elimination of generalized edema.

When one begins to understand the physiologic reasons for such phenomena as retention of salt and water, widespread arteriolar spasm, proteinuria, urinary casts, oliguria, and epigastric pain, then he becomes somewhat less frightened by these cardinal signs of preeclampsia and is less likely to institute remedial measures which offer little hope of success or which may even do further damage by interfering with vital physiologic processes. The simple therapeutic measures suggested by Dr. Page, such as sedation, sodium restriction, use of ammonium chloride to eliminate the sodium ion, injection of hypertonic sugar solutions, and possibly digitalization, all have their place in the management of the mild and moderately severe instances of preeclampsia, and certainly in a majority of patients these measures will suffice. I am, however, somewhat skeptical about the virtues of using either serum albumin or the amino acid methionine. To be sure, methionine has been employed in certain types of liver disease, but one gathers from the internists that only indifferent success has been achieved.

Despite the obvious effectiveness of these so-called conservative measures, I would like to emphasize Dr. Page's final conclusion, namely, that removal of the cause of preeclampsia may be effected only by the termination of pregnancy. In the more fulminating cases this should be done promptly and, if necessary, by cesarean section. That is to say, when any other choice as to mode of delivery would necessarily involve the passage of an indefinite period of time, then cesarean section is chosen because it offers complete control of the time factor. In this regard, I would be interested in knowing whether Dr. Page believes that delivery by section, as he intimated early in this paper, always is contraindicated in the patient who has had a convulsive seizure. I have thought it somewhat illogical to abandon on such arbitrary grounds a therapeutic measure of real value (when properly executed under suitable types of anesthesia). Are there secure reasons for saying that it is perfectly legitimate to perform cesarean section now, when the patient in question is suffering from preeclampsia, but that the advent of one or two convulsive episodes within the following hour makes it mandatory that delivery be effected at all cost by some other and often less certain method? I think obstetrics has advanced to the point where we may bring this old textbook dictum into broad daylight and scrutinize the factual data upon which it is based.

Schneider's suggestion, based upon his experimental work with mice, that thromboplastin is the culprit in eclamptogenic toxemia is most intriguing but lacks confirmation. The very recent report by Maeck and Zilliacus (American Journal of Obstetrics and Gynecology, February, 1948) of results achieved in one patient treated with heparin seemed to me not particularly convincing, although it is only fair to say that Dr. Page's experience with heparin in a small series of patients has been at least moderately encouraging. Yet I am sure he would agree that the thromboplastin hypothesis has scarcely emerged from the realm of experimentation and any recommendation for the widespread use of heparin in preeclampsia would at this time be premature if not actually dangerous.