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Studies on so-called protective ferments—X. Some suggestions as to the etiology and treatment of eclampsia.

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PRELIMINARY COMMUNICATION

Many theories concerning the etiology of eclampsia have been advanced. For certain of them there is more or less experimental and clinical evidence. The treatment, however, remains purely empirical. Each theory has as its basis that the eclamptic seizure is due to toxin developed as the result of pregnancy. As to the origin of this toxin, the authors vary to as great a degree as do the theories. The development of this toxin may be due to:

(*a*) A growing ovum and its metabolic products.

(*b*) Functional changes in the liver resulting from pregnancy.

(*c*) General metabolism being affected during pregnancy with the result that the food stuffs are not cared for properly.

(*d*) The advent of the study of parenteral digestion of foreign protein by specific ferments suggested another possibility that the toxins originate from the detached elements of the placenta as a result of their specific parenteral digestion.

The numerous attempts that were made to demonstrate by experiment the presence of this toxin in the blood were not successful. My recent experiments[1, 2] have demonstrated that pregnant serum can be rendered toxic to homologous animals by being kept for a definite time in contact with placental tissue. The toxic symptoms produced by the introduction of such a serum into an experimental animal closely resemble those generally known as anaphylactic shock. On the other hand, the injection of soluble placental protein into the blood circulation of pregnant guinea-pigs produces similar symptoms.[3] Further experiments

[1] Bronfenbrenner, *Bioch. Bull.*, 1914, IV, No. 13, p. 87.

[2] Bronfenbrenner, PROC. SOC. EXP. BIOL. AND MED., 1914, Vol. XII, p. 48.

[3] Bronfenbrenner, *Journ. Exp. Med.*, 1915, XXI, p. 480.

have shown that the mechanism of the formation of toxin is that of autodigestion of the serum with the formation of toxic split products.[4] This autodigestion is made possible through the liberation of non-specific proteolytic enzyme normally present in the blood of every animal.[5] These results seem to suggest another theory of the causation of eclampsia.

The development of the ovum is accompanied by metabolic changes in the body directly connected with the requirements of this new growth. In addition, the penetration into the general circulation of detached cells of the developing embryo together with the metabolic products of the growing fetus, sets up a new specific process of parenteral digestion of these substances in the body of the mother. As the gestation progresses and the products of the new growth repeatedly penetrate the general circulation they cause the appearance of specific antibodies of a cytolytic nature. My experiments suggest that such antibodies by combining with the antigen change the balance of the blood constituents so as to allow the liberation of the serum trypsin, which in turn digests the antigen circulating in the blood.[6] This trypsin, however, is capable of digesting also the serum itself. The products of such autodigestion of serum are very toxic and when they occur in early pregnancy they may induce symptoms of nausea, dizziness, general depression and so forth. If the amount of toxin produced by this autodigestion of serum goes beyond the limit of tolerance for the individual, acute symptoms of anaphylaxis result and we witness the eclamptic convulsions.

Normally the intoxication from the split products of such autodigestion is prevented by at least two independent processes. One is the overproduction of antitrypsin, which prevents the excessive autodigestion of serum by neutralizing the proteolytic ferments; the other is the elimination of toxic substances through the liver and kidneys which retain these toxins and, therefore, show signs of local involvement long before the general symptoms are noticed. That the antitrypsin of the blood is involved in this process was shown in this laboratory by the actual measurements[7]

[4] Bronfenbrenner, PROC. SOC. EXP. BIOL. AND MED., 1914, XII, p. 7.

[5] Bronfenbrenner, *Journ. Exp. Med.*, 1915, XXI, p. 221.

[6] Bronfenbrenner and Scott, PROC. SOC. EXP. BIOL. AND MED., 1915, XII, p. 137.

[7] Full records of these experiments will be published in the near future.

of the antitryptic index in a series of cases of eclampsia. These measurements revealed the fact that in all cases of eclampsia the patients show a very low antritryptic index. In cases where the surgical intervention took place, the antitryptic index shows very marked rise after the emptying of the uterus.

In cases where the convulsions were intermittent, spaced with periods of comparative rest, a very noticeable curve of antitrypsin in the blood could be established. The lowest points on this curve corresponded very suggestively with the convulsions. It is the high amount of antitripysin in the blood, which is so characteristic in normal pregnancy, that prevents usually the excessive autodigestion and resulting eclampsia. In abnormal cases, where the antitrypsin is unusually low, or, where the elimination is insufficient, or where both conditions are present at the same time, the general intoxication occurs.

A critical review of the methods of empirical treatment seems to me to offer considerable additional support to the above suggestion of the etiology of eclampsia. The methods of treatment of eclampsia may be considered under four headings: (1) Administration of anesthetics and sedatives, such as ether, chloroform, morphin, chloral, and similar drugs. (2) Serum treatment. (3) Eliminative treatment. (4) Surgical treatment.

Experiments carried out in this laboratory[8, 9] have shown that the administration of anesthetics and sedatives is followed by a more or less pronounced rise of antitrypsin in experimental animals, thus suggesting the possibility that the therapeutic value of these substances might be dependent on their ability to cause the rise of antitrypsin.

As for the serum treatment, Wolff[10] suggested that the therapeutic value of the injection of the serum from normal pregnant individuals, has a decided therapeutic effect, which is due to the specific protective ferments contained in the injected serum. The fact, however, that on the one hand normal human serum from non-pregnant individuals, as well as normal horse serum, were both successfully used for this purpose;[11] on the other hand, our

[8] Bronfenbrenner, PROC. SOC. EXP. BIOL. AND MED., 1915, XII, p. 110.

[9] Bronfenbrenner and Schlesinger, *Journ. Exp. Med.* (in press).

[10] Wolff, *Berl. klin. Woch.*, 1913, No. 13, p. 1661.

[11] Freund, *Deut. med. Woch.*, 1913, No. 24, p. 1179.

recent findings, showing that there are no specific ferments in pregnancy,[5, 12] exclude the explanation given by Wolff. It is known, however, that every normal serum is antitryptic, and especially during pregnancy the antitryptic titer of the serum is very high. Therefore, it is possible that the therapeutic value of such serum depends on its antitryptic property.

Eliminative treatment and surgical intervention remove respectively the toxic split products of autodigestion, and the source of the invading material, which alone sufficiently explains their action.

Considered from the above point of view, the relation between the etiological factors involved and the clinical treatment of eclampsia may be thus graphically represented:

TABLE.

Gestation—Antibody Formation.

Antibody Formation Normal	Antibody Formation Deficient. Formation of various amounts of toxic split products.
Normal Pregnancy.	Early Symptoms of Toxemia.

Good Elimination.		Poor Elimination.	
Sufficient Antitryp.	Deficient Antitryp.	Sufficient Antitryp.	Deficient Antitryp.
Slow autodigestion. Poisons eliminated.	Autodigestion pronounced. Poisons eliminated.	Slow autodigestion.	Marked autodigestion.
Symptoms very mild.	Symptoms more marked. Possible involvement of liver and kidneys.	Mild symptoms. Possible involvement of liver and kidneys.	Severe symptoms. Acute involvement of liver and kidneys.
No treatment.	Antitryptic serum treatment.	Eliminative treatment.	Combined antitryptic and eliminative treatment. Possibly surgical intervention.

[12] Bronfenbrenner, PROC. SOC. EXP. BIOL. AND MED., 1914, XII, p. 3.