The severe constitutional symptoms appearing in the course of infantile diarrhoea form a characteristic picture referred to as toxicosis. The most prominent features of this toxic condition are medical shock, acidosis, acidic breathing, functional failure of the kidneys and characteristic nervous symptoms. Clinically the nervous symptoms are characterized by extreme prostration, sometimes preceded by great restlessness. In severe cases there is complete loss of consciousness similar to uraemic or diabetic coma. Frequently cataleptic features are seen, such as the 'fencing position' of the extremities and fixation of the eyeballs. There are signs of disturbance of the autonomic nervous system, and the purpose of this paper is to analyse the origin of these nervous symptoms.

Originally the direct effect of dehydration on the brain was thought to have a bearing on the origin of the nervous disturbances (Bessau, 1921). The water content of the brain was, however, found to be normal.

That acidosis is not responsible for the severity of cerebral symptoms is shown by the fact that acidosis may be corrected by bicarbonate solutions while the cerebral symptoms may persist (Csapó and Wollek, 1935). On the other hand, death frequently occurs in spite of correction of the acidosis (Hartmann, 1928).

In Germany for the last two decades the theory of Bessau and Rosenbaum (1928) has been widely accepted. Dehydration was thought to increase the permeability of the 'blood-liquor barrier,' and result in endotoxins originating from coli or dysentery bacilli gaining access to the brain tissue.

Histological changes of the brain tissue have been described and have been considered to be of aetiological importance (Goldzieher, 1930; Schafferstein, Popowa, and Owtscharenko, 1935; Marquézy and Ladet, 1938; Kramár and Miskolczy, 1940; Christensen and Biering-Sørensen, 1946). The meninges were found to be injected and oedematous. In the parenchyma the dilated capillaries were encircled by oedematous, loosened brain substance. There was evidence of cellular degeneration amounting in some cases to necrosis. As leucocytic inflammatory changes have been absent, the picture has often been called encephalosis.

On the other hand, one of us (Kerpel-Fronius, 1947) reviewing evidence based on the pioneer work of Marriott (1920), Gamble (1928), and others, emphasized again that toxicosis is primarily a condition similar to medical shock. The failure of circulation may or may not be due exclusively to anhydremia.

A fundamental feature of medical shock is the slowing of the peripheral blood flow, thus resulting in a condition of anoxia of the stagnant type. Marriott (1920) and Utheim (1920), using a calorimetric method, measured a diminished blood flow to the extremities per unit of time in infantile toxicosis. Thus it is to be expected that the blood supply to the brain may also be diminished. We have attempted to verify this assumption. If the blood supply to the brain be diminished, the oxygen saturation of the venous blood leaving the brain should decrease. The extent of this anoxia, if a consequence of medical shock, should be related to the extent of the slowing of the blood flow. Finally it remained to be seen whether the expected anoxia had or had not a bearing on the origin of the nervous symptoms. For this purpose oxygen saturations of the cerebral blood were determined in clinical cases varying from mild dehydration to deep coma, the degree of anoxia being compared with the severity of the nervous symptoms.

Methods

Arterial blood was drawn under oil from one of the arteries of the head or arm. Venous cerebral blood was taken from the longitudinal sinus. The oxygen content of the blood was determined by Van Slyke's method. Circulation time was measured by injecting Congo red dye into the left cubital vein, another needle being simultaneously inserted into the right cubital vein. At intervals of exactly three seconds blood was withdrawn into heparinated glass capillaries. After the separation of the plasma from the corpuscles, the first appearance
of the dye was clearly visible. The time elapsing from the injection to the first appearance of the dye in the vein of the corresponding arm is the circulation time.

Results

Fig. 1 shows the oxygen saturation in the arterial and cerebral venous sinus blood of 11 dehydrated infants.

![Graph showing oxygen saturation in arterial and cerebral venous blood](image)

**A** = arterial oxygen saturation  **V** = venous oxygen saturation.

Fig. 1.—Diagram showing oxygen saturation in the arterial and cerebral venous (sinus) blood of 11 dehydrated infants and one normal.

Each column represents an individual case. Reading the figure from left to right, cases are progressively more severe. The figure shows that parallel to the increasing gravity of the clinical condition, the arteriovenous oxygen difference is progressively greater. That is a proof of slowed cerebral circulation.

It is also seen that the oxygen saturation of the blood of the longitudinal sinus is becoming progressively less in cases of increasing severity. The cerebral symptoms characteristic of the toxic phase of dehydration appeared when the oxygen saturation of the cerebral venous blood approached 25%. Deep coma was observed when the latter decreased to less than 15%.

In a number of cases arterial oxygen saturation is also somewhat lowered. That is probably due to paravertebral pulmonary congestion. Low arterial oxygen saturation is obviously disadvantageous when superimposed on anoxia of the stagnant type. It is thus comprehensible that in infantile dehydration intercurrent pneumonia greatly facilitates the appearance of toxic symptoms.

Fig. 2 shows the circulation times plotted against cerebral venous oxygen saturations. The close correlation between decreased oxygen saturation in the cerebral venous blood and medical shock as measured by circulation time is clearly visible. The longer the circulation time, the severer the cerebral anoxia. The cerebral symptoms characteristic of toxicsosis appeared at an approximately trebled circulation time of about 40 seconds; at this point we invariably found oxygen saturations below 25%.

Discussion

Our data reveal that the cerebral symptoms in infantile toxicsosis appear when the degree of venous anoxia reaches a certain point. That this anoxia is of aetiological importance in the genesis of the comatose condition can be confirmed by the following data. In anoxia due to a slowed circulation each portion of blood gives up a larger proportion of its oxygen load in the proximal capillaries. Consequently in the more distal capillaries a large part of the oxygen is delivered under low pressure.

As oxygenation is a function of pressure, a large part of the brain will receive insufficient amounts of oxygen. In this respect the work of Lennox, Gibbs, and Gibbs (1935) is of great interest. These authors studied the relation of unconsciousness to the supply of oxygen in normal adults, inducing lack of oxygen by breathing nitrogen or by experimental syncope. Unconsciousness resulted in every case when the oxygen saturation of the blood from the internal jugular vein was less than 30%. It may be seen that this figure closely corresponds to our figures as found in the blood of the longitudinal sinus in toxicsosis. Fig. 3 gives additional data, and shows that in infantile bronchopneumonia, where the anoxia is chiefly arterial, unconsciousness results when about the same degree of cerebral anoxia is reached as in toxicsosis or in artificial syncope.

The construction of Fig. 3 corresponds to that of Fig. 1.

It may be seen from our six cases of infantile
bronchopneumonia that the arteriovenous oxygen difference is generally normal; thus, in contrast to toxicosis, the velocity of cerebral blood flow is unchanged. The arterial oxygen saturation due to insufficient oxygenation in the lung is, however, so low that in severe cases the oxygen saturation of the blood of the longitudinal sinus is as low as in toxicosis. In the latter case, bronchopneumonia was accompanied by unconsciousness.

Coma, probably due to lack of oxygen, may in certain conditions be of a more complicated origin and can be revealed only by measuring the oxygen consumption of the brain. Kety et al. (1948) have found that in diabetic acidosis coma was associated with, and probably the result of, a 40% reduction in cerebral utilization of oxygen which occurred in spite of a generally augmented cerebral blood flow and normal oxygen saturation. Thus coma seems to result both in diabetes and toxicosis from the same mechanism, namely, the lack of oxygen. The latter is brought about in toxicosis chiefly by simple slowing of circulation, i.e. by shock, while in diabetes more complicated factors are operating. Last, it should be remembered that the cerebral signs of toxicosis have some features in common with the picture of lack of oxygen as observed in studies of aviation medicine.

The very low oxygen saturation in cerebral venous blood may have a bearing on the origin of some of the histological changes described in the brain of dehydrated subjects. Henry, Goodman, and Meehan (1947) studying arm veins of adults, found that in conditions in which the venous oxygen saturation falls below a critical level of 25 to 15%, a significant increase in permeability to protein occurs. The pericapillary oedema in the brain of toxic infants may thus be a sequel of anoxia.

**Summary and Conclusions**

The oxygen saturation of the blood of the longitudinal sinus was determined in 11 dehydrated infants. The oxygen saturation decreased parallel to the gravity of the clinical condition. A close correlation was found between the decrease of the oxygen saturation of the cerebral venous blood and anhydreaemic shock as measured by circulation time. The longer the latter, the lower the oxygen saturation of the former. The cerebral symptoms characteristic of a toxic condition in dehydration appeared when the oxygen saturation of the cerebral venous blood approached 25%. Deep coma was observed when the latter decreased to less than 15%. Thus, the cerebral symptoms of severe dehydration appear to be due to cerebral anoxia of the stagnating type.

**References**

Baltimore, p. 257.