SENSITIVITY TO COW'S MILK PROTEINS IN ACUTE GASTRO-ENTERITIS

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The high mortality of acute gastro-enteritis in infants makes urgent the problem of elucidating its exact causation and nature. Between the years 1927 and 1932, of 170 infants admitted under the care of the Children's Department of the London Hospital who suffered from this condition, 73 died, giving a mortality rate of 43 per cent. If the very mild cases are excluded from this series, the death rate becomes 77 per cent. These figures are not dissimilar to those occurring in most other hospitals.

The intestinal lesions found at autopsy in these cases are as a rule not in themselves sufficient to account for death, and it is probable that they are frequently the result rather than the cause of the diarrhoea. Alimentary infection, often preceded by unsuitable feeding, is known to be frequently responsible for the onset of acute gastro-enteritis, but it is also recognized that in many cases gastro-enteritis is associated with a focus of infection—which many regard as primary—elsewhere than in the gastro-intestinal tract. In all severe cases, however, the symptoms show that there is dehydration of the body, and profound general toxæmia. Of the nature of this highly dangerous toxæmia there is still much that is unknown.

It appears that in conditions of marasmus and gastro-intestinal disturbances in infancy the secretion of gastric juice is decreased; there is also evidence that trypsin may be deficient in infants suffering from diarrhoea. It follows that digestion must be impaired and the breaking down of proteins interfered with. It has been shown by experiments that athreptic infants and those suffering from gastro-enteritis absorb undigested protein from their alimentary tracts (Schloss and Anderson¹, Anderson and Schloss², Schloss³); both by precipitin tests and by anaphylactic experiments on guinea-pigs, these workers demonstrated that antigenic protein was absorbed into the blood in such cases.

Moreover, experiments quoted by Schloss³, which were conducted by himself and his co-workers, showed that the enteral absorption of antigenic protein leads to specific skin hypersensitivity, as demonstrated by intradermal tests. Further, Greer⁴ demonstrated by means of intradermal injections that sensitivity to cow's milk occurred in infants suffering from acute gastro-

enteritis, whereas normal infants showed no such sensitivity. The reason for this absorption of protein in wasted infants and those suffering from acute gastro-enteritis cannot be definitely stated, but probably incomplete protein digestion and increased permeability of the alimentary tract are both factors involved. Theoretically it seems possible that the fatal toxicosis occurring in severe gastro-enteritis may be associated with this absorption of relatively large amounts of foreign protein unchanged. Such a possibility has already been suggested by Schloss³ and others. It seems significant that some of the symptoms of acute intoxication occurring in severe cases of gastro-enteritis are not unlike some of those seen in protein shock.

It has been shown by Schloss³ that normal infants fed on cow's milk absorb for a short time a certain small amount of the foreign protein of cow's milk unchanged, though this is infinitely less than in the case of wasted infants, or those suffering from diarrhoea. After the ingestion of foreign protein, normal infants produce very promptly an immunity reaction, as shown by precipitin formation. The precipitin is present in the blood, however, for a short time only, its subsequent disappearance showing that absorption of antigenic protein has probably then ceased. It is therefore reasonable to suppose that normal infants rapidly put themselves in a position to deal with such protein by the production of antibodies until the absorption ceases. If, however, an infant should happen to absorb more foreign protein than it is able to cope with in such a manner, it may become allergic to the protein, the body having established only a partial defence. Should the infant now suffer a gastro-intestinal upset, there is likely to be a sudden larger absorption by the unhealthy and more readily permeable alimentary tract of unaltered protein, which has been incompletely digested owing to a diminution of the normal supply of proteolytic ferments. It is possible then that an infant who is allergic to cow's milk protein is thus suddenly exposed to the absorption of a relatively large amount, and as a result severe allergic reactions occur, which may be to a great extent responsible for the toxic symptoms. In accord with such a theory is the fact that acute gastro-enteritis is much commoner in infants fed on cow's milk than in those that are breast fed, and is especially liable to occur after rapid weaning.

As a further step in the study of this problem it was therefore decided—assuming, on the basis of previous work, that foreign protein had been absorbed by those infants suffering from acute gastro-enteritis—to try and ascertain whether or not they had become sensitive to such foreign protein. With this in view an attempt was made to determine whether or not reagins were present in the blood of these infants, rendering them allergic to cow's milk. For this purpose the Prausnitz-Küstner reaction was employed. This consists in transferring sensitivity to a given antigen to the skin of a previously insensitive person, by means of an intradermal injection of serum from a subject himself allergic to this antigen. This passive transfer reaction would, if positive, show that reagins were present in the blood of the infants concerned, and thus demonstrate that they were sensitive to the antigen in question.

Experimental procedure.

About 5 c.c. of blood was taken from the superior longitudinal sinus of each of 18 infants under the age of 9 months, suffering from gastro-enteritis in the acute stage. The majority were severely ill, 11 dying within a relatively short time. No infant that was breast fed was included in the series, and all had, so far as it was possible to ascertain, received various types of cow's milk feeding only. No mixed feeding had been commenced, therefore any foreign proteins that might have been absorbed would be those of cow's milk only.

After withdrawal in a dry syringe, the blood was defibrinated by shaking with glass beads in a bottle, and then centrifuged. The serum was pipetted off, put up in ampoules ready for use, and stored in an ice chest. The Wassermann reaction was carried out on each child's serum; it was found to be negative in all cases.

The subjects on whom the test reaction was carried out were convalescent male patients whose general medical condition was good. As a preliminary to each experiment, the subject was skin-tested by the scratch method with an extract of whole cow's milk protein, in order to ascertain that he did not exhibit sensitivity to cow's milk. Prior to commencing the test, all milk was excluded from his diet for approximately 24 hours. An intradermal injection was then made, in the flexor surface of the upper arm, of 0.075 cc. of the infant's serum to be tested; in certain cases the serum had previously been diluted with saline, in others it was used undiluted. At first a 1 in 5 dilution was used, but it was soon decided to use a greater concentration. Twenty to twenty-four hours later, the sensitized site and a control site were each injected with 0.04 c.c. of antigen. The antigen used in most instances was a lactalbumin extract* (since it is known that sensitization is more commonly produced by lactalbumin than by casein), but in certain experiments whole, sterile cow's milk was employed.

After injection of antigen, readings were taken at the end of $\frac{1}{2}$ hour, 1 hour, 2 hours, 3 hours, and then again on the following day.

The serum utilized was, as already stated, obtained in the acute stage of acute gastro-enteritis. In practically every instance, more than one test was made with each serum; owing to the small quantities of serum available, it was not possible to test each serum both diluted and undiluted, and with each of the antigens mentioned.

The results of 42 Prausnitz-Küstner reactions, as carried out upon the above lines, are shown in the following table.

Discussion.

Admittedly the above investigation, carried out on a relatively small series of cases, is not conclusive, and in certain instances the results obtained from the injection of one serum into two different subjects were at variance. Of the 18 infants whose sera were tested, 8, however, gave completely positive results, while only 2 cases (1 and 6) gave consistently negative results. Five (cases 5, 9, 11, 14 and 15) gave results that were positive in one or more tests, but equivocal in others. The remaining 3 (cases 2, 8, and 12) gave contradictory results. Of the whole series of 42 Prausnitz-

* The lactalbumin extract employed was obtained from Messrs. Duncan Flockhart and Co.

	Serum diluted 1 in 5. Lactalbumin extract diluted 1 in 2.	Serum diluted 1 in 2. Lactalbumin extract diluted 1 in 2.	Serum diluted 1 in 2. Whole cow's milk.	Serum undiluted. Lactalbumin extract undiluted.	Serum undiluted. Whole cow's milk.
1. G. B.	—	—	—		
2. P. B.	+	—			
3. E. K.	++	+	(a) ++ (b) ++		
4. B. W.		+			
5. T. V.		(a) $\pm$ (b) +			
6. R. C.		(a) — (b) —			
7. S. M.		(a) + (b) ++			
8. M. D.		(a) — (b) ++ (c) $\pm$	++		
9. J. W.			(a) + (b) $\pm$		
10. C. M.			(a) ++ (b) ++		
11. W. B.			(a) $\pm$ (b) ++		
12. P. R.			+		(a) + (b) —
13. S. de B.				+	
14. J. S.				(a) $\pm$ (b) + (c) $\pm$ (d) $\pm$	
15. D. O.				(a) + (b) +	
16. R. P.				(a) $\pm$ (b) +	
17. J. A.					(a) ++ (b) +
18. S. G.					(a) ++ (b) ++

The small letters (a), (b), etc., are used to indicate that more than one test was performed.

Küstner reactions carried out, 61.9 per cent. gave definitely positive results, and only 19 per cent. were definitely negative. This, especially when taken in connection with previous work already quoted, is significant. It may be noted that, although Greer⁴ found that it was chiefly to lactalbumin that sensitivity occurred, the more strongly positive results were, generally speaking, obtained in the above experiments when whole cow's milk was employed as antigen.

Conclusions.

It appears from the experiments carried out that reagins to cow's milk proteins are frequently present in the blood of infants suffering from gastro-enteritis. From this one may conclude that many such infants are hypersensitive to cow's milk proteins.

It is possible that some of the toxic symptoms of acute gastro-enteritis may be in the nature of an allergic reaction.

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