Association of Vitamin B_6 Deficiency With Convulsions in Infants

By E. M. NELSON, Ph.D.

ONE WAY in which the Food and Drug Administration protects the consuming public is by monitoring the recovery from trade channels of any product, food, drug, or device that is found unsafe for use.

In 1953 such a program related to the occurrence of a series of cases of convulsions in infants that had been maintained on an infant food called SMA Liquid Formula (for convenience termed SMA liquid). The Food and Drug Administration's part in correlating the observations on these cases and in concluding that the condition was the result of a deficiency of vitamin B_6, although discussed at a conference on vitamin B_6 in human nutrition (*1*) and referred to by May (*2*), is not reflected in several other published reports of these cases (*3–7*).

Through its inspectors, the Food and Drug Administration assembled hospital records of a large number of affected infants. After careful study of these records by its medical and scientific staff and consideration of information gained from the manufacturer of the SMA liquid, particularly with respect to changes in composition of the product, it was possible to recognize interrelationships not apparent to the pediatricians who attended the individual cases.

Although at the time a confidential statement containing this information was submitted to the National Institutes of Health, the Food and Nutrition Board, and the Council on Foods and Nutrition of the American Medical Association, it may be well to set forth, for a wider audience, the sequence of events that led to a recognition of the relation of vitamin B_6 to the infant convulsions. It is hoped that this will encourage prompt reporting of any unexplained disease condition that may be related to ingestion of a food or use of a drug, thereby enabling the Food and Drug Administration to take remedial steps at the earliest possible stage to safeguard the public.

Early in December 1952, the Food and Drug Administration received a letter from an Arkansas resident, a trained nurse, whose 3-month-old infant had developed convulsive seizures. She gave a complete and informative case history of her child, who had been fed SMA liquid from birth. The attending pediatrician apparently suspected the condition was associated with SMA liquid because he immediately changed the formula to evaporated milk and Karo syrup. Complete recovery from the convulsions resulted from this change. The mother then learned of eight similar cases in her community, all associated with the use of SMA liquid. All of the infants recovered from convulsions following a change of formula.

A short time later the director of the Arkansas Division of Food and Drug Control discussed the problem with our St. Louis district office, asking if we had received consumer com-

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plaints about SMA liquid. The manufacturing firm, we learned, was aware that the product was associated with infant convulsions. Of the 12 cases reported to the firm the majority had occurred in Arkansas and northern Texas, and the firm attributed the condition to a change in mineral content of water used to dilute the product for feeding. There had been a severe drought in the Arkansas-Texas area, and the attention of the firm was focused on a possible mineral imbalance that might cause the tetany-like syndrome.

Accumulative Evidence

In investigations during January and February of 1953, the Food and Drug Administration developed the following facts:

1. More than 50 cases of so-called SMA convulsions had occurred.

2. At this stage the majority of cases had been found in the Arkansas-Texas area.

3. Invariably the sick infants had been fed SMA liquid with no vitamin supplements. Similar symptoms and physical signs were noted in the affected infants. These included hyperirritability (particularly sensitivity to noise), diarrhea, and vomiting (frequently projectile), followed by convulsive seizures lasting from one-half to 5 minutes, and recurring from once or twice daily to as many as 11 times daily. Rectal temperatures ranged from 99° to 101° F.

4. The convulsions appeared in infants ranging in age from a few weeks to nearly 1 year.

5. The formula for SMA, both powder and liquid, had been changed some time prior to January 1952 by replacing the coconut oil in the fat by palm oil.

6. All cases of convulsions were traced to the new SMA liquid formula by codes containing the letters "H" or "I".

7. In every case reported there was relief from the convulsions when the food formula was changed.

8. No cases of convulsions were reported from the use of powdered SMA, which had the same basic composition as the liquid.

9. Sedatives relieved the convulsions some, but no other medication was effective.

10. There was no clue as to the causative agent from chemical examinations of blood and urine or from clinical tests or clinical trials.

11. Samples of the product were found to be sterile.

12. Chemical examination of the product revealed nothing unusual.

13. Many of the infants whose case records came to our attention had been under the care of pediatricians, and thorough studies had not established the etiology of the convulsions.

14. Records of such cases were not found in those larger cities where hospitals were surveyed by food and drug inspectors.

Late in March 1953, in the Food and Drug Administration, the files on this subject were referred to the Division of Nutrition for study. It was noted that the irritability and convulsive seizures described in the case records resembled the symptoms in rats from mothers on a vitamin B_6 deficient diet that had been observed in the division's laboratories (*8*). The rapidity of the infants' response to a change in the formula was also characteristic of the animals' recovery from symptoms of deficiency with a change to an adequate diet. Such a prompt response is not usually observed in the treatment of a toxic condition.

The composition of SMA liquid was also a basis for suspecting nutritional deficiency. The product was made from skimmed milk to which fats, lactose, vitamins A, D, C, B_1, B_2, and niacin, and potassium carbonate and ferrous sulfate were added. The reduced proportion of milk solids was supposed to provide a level of protein simulating that of mother's milk, although with such modification the amounts of water-soluble nutrients of milk, including vitamin B_6, were similarly reduced.

Dr. O. L. Kline of the Division of Nutrition was the first to associate the symptoms observed with vitamin B_6 deficiency and to offer an explanation that was in harmony with all of the facts developed. That was in March 1953, more than 6 months after the first cases occurred and after 50 or 60 cases had been treated by physicians in many areas of the country. But if vitamin B_6 deficiency was the true cause of convulsions in the infants, two questions had to be answered: First, in what manner could the substitution of palm oil for coconut oil influence the vitamin B_6 content of the product

or requirements of the infants for this vitamin? And second, why should the deficiency occur with SMA liquid and not with SMA powder which had the same composition?

The Solution

The replacement of cocónut oil by palm oil in the SMA products was based on the demonstration that this change resulted in stools that, in many respects, more nearly simulated the stools of breastfed infants. A substantial change was also observed in the intestinal flora, with a marked increase in numbers of *Lactobacillus bifidus*. Obviously, either the population of organisms requiring B_6 may be increased or the population of organisms that produce vitamin B_6 reduced as a result of this change in the fatty constituents of the product. Three studies reported in 1938 show an important relationship between vitamin B_6 requirement and the fat in the diet with particular reference to the nature of the unsaturated fatty acids present (*9*). Witten and Holman (*10*) have presented evidence that in the rat there is a need for pyridoxine for the synthesis of the more highly unsaturated fatty acids.

Experiments in our laboratory had indicated that although pyridoxine hydrochloride is stable when autoclaved at 15 pounds pressure at a pH of 7, the vitamin B_6 in natural products is reduced substantially by such heat treatment. Pyridoxal and pyridoxamine, forms of vitamin B_6 that occur in food, are types of compounds known to react, upon heating, with amino acids and sugars to form a complex which the animal cannot fully use (*11*, *12*). SMA liquid is subjected to a process of heat sterilization, but SMA powder is not. Therefore, the liquid product may be expected to be lower in vitamin B_6 content than the powder.

In examining SMA liquid for vitamin B_6 content, we were unable to obtain satisfactory results because the chemical method in use for the examination of pharmaceutical products was not applicable to milk products. Attempts to produce convulsions or other evidence of vitamin B_6 deficiency in rats were unsuccessful since the low protein and high lactose content of the product are not adapted to the nutritional requirements of the rat.

More recent analytical evidence has clearly demonstrated that SMA liquid contained a lower level of vitamin B_6 than similar liquid infant formulas, and less than the amount found in the SMA powder. This confirmed our suspicion based upon knowledge of the composition and effect of processing.

A careful resurvey of the case records of the infants affected showed that in the few instances vitamin supplements had been used none of them contained vitamin B_6.

The general causes of convulsions in infants and the plausibility of the explanation offered in this instance were discussed with Dr. Irvin Kerlan and Dr. Leo Parmer of the FDA Division of Medicine. This discussion led to the referral of some of the case histories to Dr. L. Emmet Holt since he and his associates (*13*) had reported studies of vitamin B_6 deficiency in infants. After reviewing these cases, Dr. Holt expressed the view that the symptoms described resembled those he had observed. The Division of Medicine then urged pediatricians to test clinically the effect of pyridoxine hydrochloride in infants showing SMA convulsions without changing the feeding formula.

Early in May investigations of hospital records revealed the occurrence of more than 50 cases of SMA convulsions in the vicinity of Lancaster, Pa. Additional occurrences were reported at Walter Reed Hospital in Washington, D. C., brought in from widely separated Army installations. Also, called to our attention were reports of three new cases in areas where it was thought the offending product had been replaced by a new formula. A more effective and complete recall of codes under suspicion began on May 15. Two weeks later a nationwide check by the Food and Drug Administration to determine the thoroughness of this recall indicated that it was reasonably complete, although there were instances in which confusion arose in identifying the codes and in which there was some uncertainty about the amounts in the hands of individual purchasers. More than a million cans of the suspect product were removed from the market.

On May 29 the Food and Drug Administration was advised by telephone that Dr. Charles D. May of the University of Iowa had treated an infant showing SMA convulsions by intra-

muscular administration of pyridoxine hydrochloride, while maintaining the infant on the SMA liquid. The infant recovered completely from convulsions. This report was confirmed by letter from Dr. May a few days later. Confirming reports from other investigators followed within a short time. With confirmation of the relationship of SMA convulsions and vitamin B_6 intake in infants, the manufacturer added pyridoxine hydrochloride to the product. It appears that several weeks were required for complete replacement of old stocks, since we learned of a few cases of the illness as late as September 1953, even after the palm oil was eliminated and the old formula reestablished (*14*). In the succeeding 2 years no additional occurrences of convulsions were reported.

It is significant that the majority of cases of infant convulsions occurred in rural areas rather than in the larger cities where the large proportion of infants are under the care of pediatricians. The prevailing practice by many pediatricians of supplementing liquid formulas with solid foods and vitamin preparations at an early age may not be followed in some rural areas. It is significant, also, that more than a hundred cases of vitamin B_6 deficiency occurred in this country before the condition was recognized as a deficiency disease.

With constant improvement in food processing, acceptable methods are needed for determining the nutritional adequacy of infant foods. For products in which the lactose is increased to simulate mother's milk, the classical biological test with the rat is impracticable because of intolerance to lactose.

The Food and Drug Administration is in a particularly favorable position to assist public health officials and the medical profession in bringing under control disease outbreaks or unusual reactions that are related in any way to the use of foods or drugs. With its investigational authority and its experienced investigational staff, facts may be collected without delay for review by the medical and scientific staff. It would be helpful if there were prompt reporting to the Food and Drug Administration of occurrences of unexplained disease conditions or unusual reactions, particularly where association with the use of a particular food or drug is suspected. In such reports it is very helpful to have the complete case history and the codes or batch marks of the suspected product.

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PHS films

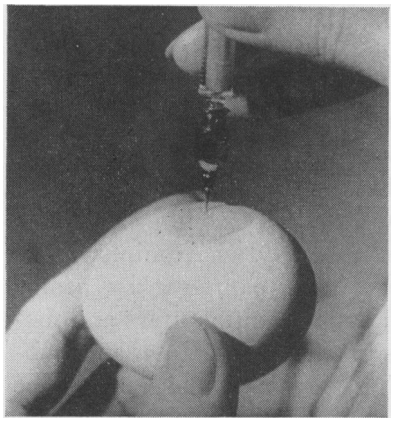
Embryonated Egg Techniques for Virus Studies

35 mm. Filmstrip, black and white, sound, 11 minutes, 59 frames, 1955.

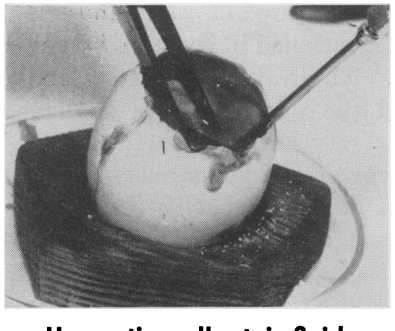
Audience: Trainees in virology techniques, virus laboratory directors, and technicians.

Available: Loan—Public Health Service, Communicable Disease Center, 50 7th St. NE., Atlanta 23, Ga. Purchase—United World Films, Inc., 1445 Park Avenue, New York 29, N. Y.

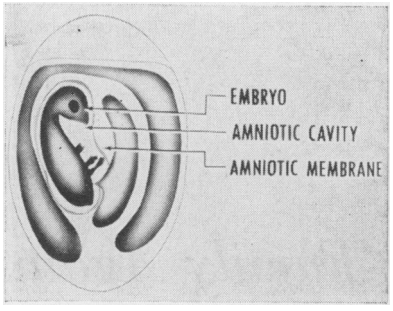
Serving as an introduction to embryonated egg methods for isolating viruses in virus laboratories, public health laboratories, and medical schools, this filmstrip illustrates several egg inoculating and harvesting techniques.



Inoculation of chorio-allantoic membrane.



Harvesting allantoic fluid.



Anatomy of embryonated egg.

Applications of these processes to the yolk sac, allantoic fluid, chorio-allantoic membrane, and amniotic cavity are pictured. Both the "window" and the direct procedure for inoculating the amniotic cavity are shown.

Disaster Aid—Public Health Aspects

16 mm. Film, black and white, sound, 11 minutes, 1955.

Audience: Health officers, sanitarians, and sanitary engineers on emergency sanitation.

Available: Loan—Public Health Service, Communicable Disease Center, 50 7th St., NE., Atlanta 23, Ga. Purchase—United World Films, Inc., 1445 Park Avenue, New York 29, N. Y.

Designed to show the methods used to solve health problems created by natural disasters, this film depicts work carried out by the Communicable Disease Center and other disaster relief agencies during flood conditions.

Emergency immunization carried out as a flood relief measure.

It documents the efforts of local, State, and Federal health agencies and emphasizes the distinct role of each in combating the dangers to public health arising from an actual flood situation.

Mobile water purification unit for disaster relief.

A Plant Health Program

35 mm. Filmstrip, sound, black and white. 14 minutes, 54 frames. 1955.

Audience: Health department personnel, physicians, nurses, management, and labor.

Available: Loan—State health departments; Public Health Service regional offices; and Occupational Health Program, Public Health Service, U. S. Department of Health, Education, and Welfare, Washington 25, D. C. Purchase—United World Films, Inc., 1445 Park Avenue, New York 29, N. Y.

Interest in employee health programs is greater than ever before, and such programs are being developed in increasing numbers.

Management, labor, and the health professions are all affected, directly or indirectly, by this development. Financed by management, employee health services are provided at, or through, the place of work. More and more, they are being recognized as an indispensable means of keeping the worker healthy and on the job.

This filmstrip tells the story behind employee health services. By taking the viewer to a printing plant in Louisville, Ky., to watch an employee health program in operation, it helps to answer such questions as: Why are employee health programs being established? What services do they provide? What do they accomplish?