III. FURTHER STUDIES IN THE ACQUISITION OF HUMAN HYPERSENSITIVENESS

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In a recent work on specific sensitization the writer[1] studied the influence of the hereditary factor in a group of one thousand cases of atopy (hay-fever and asthma). The findings indicated that inheritance is the chief factor in determining whether or not an individual will ever develop clinical manifestation of hay-fever and asthma and governs very largely the time in life when symptoms will appear. It also determines to some extent the group or groups of protein to which the individual may become specifically sensitive. Results of our study also indicated that the earlier in life clinical manifestations of allergy develop the greater the tendency of the individual to become sensitive to more than one group of proteins. This work also included a review of the histories of four hundred and three normal University students who gave no history of atopy. It was found that only 9.1 per cent of the normal students had an antecedent history of hay-fever or asthma, which is in marked contrast to 60.1 per cent of all hay-fever and asthma cases studied who gave a definite history of asthma or hay fever in the antecedents. A further study of protein tests in 119 new born was made. Our first investigation revealed a positive reaction to food proteins in two of the new born cases.

It has not been definitely proved that the substance to which patient become specifically sensitive is always protein. In fact, Grove and Coca[2] have shown experimentally that the pollen atopen is a non-dialysable, non-digestible substance and is probably non-nitrogenous. However, in an undigested pollen solution the atopen content is usually in direct proportion to the nitrogenous content. For this reason nitrogen determination of the solutions are made to evaluate the relative atopic activity of the extracts. Black and Moore[3] in a study of the chemistry of pollens digested the pollen to the extent that the amount of protein left in the pollen solution would not give a reaction to the biuret test, yet there was no appreciable lessening of the atopic activity of the extracts.

The physiological chemists tell us that the proteins before they are absorbed by the intestinal tract into the blood stream are hydrolized to amino acids and are absorbed as such and circulate in the blood stream in that form. Prof. Howard B. Lewis[4] of the University of Michigan believes that protein is not absorbed through the intestinal tract in any other way than the one just mentioned. However, Dr. Edward B. Meigs[5] of the United States Department of Agriculture, Bureau of Dairying, states:

"In regard to the general question of the passage of complete proteins or large fragments of the protein molecule through the intestinal wall and through the cells of the mammary gland, I think it may be regarded as established. There is good reason to believe, however, that this passage of complete protein through the mammary gland cells and therefore through

the intestinal cells of the offspring, is reduced to nothing or almost nothing after the first few days of lactation."

Shannon[6] has shown that the proteins of human food pass into the human milk in large quantities in the early state of lactation. Black[7] relates a history of a child under his care, who was sensitive to peanuts, who had two attacks of asthma directly traceable to using milk from a cow fed on peanut hay, which is excellent evidence that either protein, or a substance, nitrogenous or otherwise, passed into the lacteals. Waltzer[8] demonstrated that unaltered protein of at least part of the egg to which the patient is sensitive could be frequently passed unchanged into the blood stream. If it can pass through the intestinal mucosa unchanged, the author sees no objection to believing that it can pass into the lacteals.

The author has observed clinically that the atopic substance in food, whether it be protein or non-protein in character, probably is absorbed by the mucous membranes of the mouth and stomach, as symptoms of a specific sensitivity will frequently appear from two to ten minutes after the patient eats a protein to which he is specifically sensitive, which is not sufficient time for digestion of proteins to take place.

Considering our observation of the clinical manifestations of atopy in the light of the present knowledge of the chemistry of digestion and the normal constituents of human and cow's milk, the writer is of the opinion that the substance to which patients become specifically sensitive is in most cases a non-nitrogenous one, probably enzyme in character.

One hundred eighty children with hay-fever and asthma, in all of whom the hypersensitive condition was demonstrated by a positive intradermal test, are now being presented along with a further study of the dermal tests for protein sensitivity in the new born. From this work we will offer additional evidence to substantiate our conclusion that a child may be born specifically sensitive. In this study we will consider only those points pertaining to the time in life when the specific sensitivity is acquired.

Of the one hundred eighty children studied, twenty-four, or thirteen per cent, developed symptoms during the first year. Of the twenty-four, only two were found not sensitive to food. Three cases developed symptoms the first day they were born, and eight cases manifested evidence of specific sensitivity while they were nursing the mother's breast, before supplemental feeding was given. Four developed allergic symptoms as soon as cream of wheat was added to the diet. Two children developed evidence of specific sensitivity on the addition of eggs to their diet. All except two of the twenty-four cases who were sensitive to food were also sensitive to inhalant proteins. A child with the inherent ability to become sensitive to foods should in the majority of cases become sensitive to inhalant proteins if the contact is adequate. It is generally considered that an individual must come in contact with a given protein either by ingestion or inhalation before he can become specifically sensitive and have hay-fever or asthma from contact with that protein. Doctors

in general practice of medicine and especially pediatricians have frequently noticed manifestations of asthma, hives or eczema as soon as wheat products, eggs, oatmeal or other foods are added to the child's diet. It is difficult for them to understand at what time the child, manifesting evidence of specific sensitivity to wheat, oats or other protein, had actually come in contact with those foods in sufficient quantity to develop a specific sensitivity. Up to the present no one has offered a satisfactory explanation of the source of contact.

We wish to present four cases for your consideration and discuss the possibility of the acquisition of a specific sensitivity to food while in utero.

Case 1. B. J. M., a girl, age 5 months, who showed symptoms of asthma and eczema at four months of age. She was nursed by the mother about three weeks, at which time, due to lack of milk supply, she was put on Eagle Brand milk, but gained poorly. Three weeks prior to the onset of symptoms her diet was changed to modified cow's milk. Her asthmatic attacks occurred daily and had persisted about one month at the time first seen by us. An antecedent family history of hay-fever and asthma was prominent. Food tests showed a four plus reaction to wheat and to no other food protein. The question of wheat contact immediately arose. The nurse accompanying the baby informed us that the milk supply came from a cow fed on bran. This child was put on milk coming from cows fed on green wheat pasture with the result that she became symptom free. This case has been under observation the past two years. The mother has reported a number of attacks of asthma and hives following the eating of a small piece of bread.

Two questions naturally present themselves. First, when did the child become specifically sensitive to wheat second, what was the source of the wheat protein that was causing her asthma? In answering the first question, there are only two possibilities. First, she was either born specifically sensitive, or split products of wheat, or some products, probably non-nitrogenous in character, came down through the mother's milk, or through the cow's milk, thereby bringing her in contact with them to the extent that it was possible for her to develop a specific sensitivity. Only one answer to the second question can be given,—a substance to which she was specifically sensitive came down through the cow's milk.

Case 2. M. F. B., a girl, age 3 years, developed hives associated with a severe diarrhea at four days of age. At three weeks of age eczema appeared and at three months asthma manifested itself and has occurred almost daily for the past two and one-half years. At the time that all three symptoms mentioned developed the diet was that of mother's milk. Several members of the family, one being the father, had had asthma. Cutaneous tests proved the child to be four plus sensitive to both eggs and wheat. Clinically eggs and wheat were the cause of her symptoms as removal of these foods freed the child.

Again two questions naturally arise. First, when did this child become sensitive to eggs and wheat; second, what was the source of the egg and wheat protein that was causing her symptoms? There are two possible answers to the first question. First, it is possible

that she received enough wheat and egg protein through the mother's milk supply during the first three days of life to allow her to become sensitive to wheat and egg protein, or some non-nitrogenous substance associated with them, and the specific food sensitivity was the cause of her symptoms at four days of age, but it is not very probable. The other answer is that she was born specifically sensitive to wheat and egg protein, and it is the author's judgment that this is what actually happened. The source of the egg and wheat protein that continued to cause symptoms was undoubtedly some form of protein or other substance from the above products that appeared unchanged in the mother's milk, inasmuch as no other food had been taken when the first symptoms appeared.

Case 3. L. M., a boy, age 18 months, who showed typical asthmatic wheezing the first day he was born, and such symptoms appeared almost daily during the past 18 months. The grandparents on both sides of the family had asthma; the mother had hay-fever. Protein tests revealed a four plus reaction to wheat and eggs. Elimination of these two foods freed him of asthma and he has continued to remain free during the past eight months.

The chief question in this case is when did he become specifically sensitive to wheat and eggs? There is logically only one answer. He was born specifically sensitive.

Case 4. D. H., a boy, age 9, with a history of typical asthmatic attacks since he was two days old. The mother reports that on the second day he had difficult breathing and her physician told her that it appeared to be asthmatic in type. At intervals since that time the same type of breathing has occurred and the last couple of years it has been very severe. Protein tests done by the intradermal method showed a three plus reaction to wheat, peanuts, apples, plums and canteloupe. He was nursed by his mother until he was 7 months of age and during the time he was nursing he had typical attacks of spasmodic breathing, with bronchitis. When cream of wheat was added to his diet at 7 months of age, and especially at three years of age when he began to eat various types of food, including nuts, his attacks became very severe.

The question naturally arises in this case,—when did he become specifically sensitive? It seems that there is only one answer, and that is, he was born specifically sensitive.

The cases just reported in detail and the history of allergic symptoms which followed immediately upon the addition of food protein to the nursing baby's diet, in many of our food sensitive patients, is clinical evidence that children are born specifically sensitive to food proteins, or some substance, nitrogenous or non-nitrogenous, in many cases, and that they may receive enough protein or some substance other than the normal protein constituent of mother's milk or cow's milk, to allow them to become specifically sensitive through that channel.

Neither in our previous study nor in the present is there any evidence that the specific sensitivity is inherited, but the ability to become so is inherited. The type of sensitivity the antecedents suffered from has no relation to the type the descendant may have. One may

have hay-fever from Bermuda pollen and the other asthma from chicken feathers. The individual inherits the tendency and not the specific state. The germ cell is not affected. The transmission of the ability to become sensitive seems to follow Mendel's law. Whether the nature of the inheritance is as single dominant factor or a recessive on will require further study.

As a means of substantiating or disproving the correctness of our conclusion from clinical evidence that a child may be born specifically sensitive, we studied the cutaneous food tests in 119 babies before they were three days old. Most cases were tested on the second day. The food proteins used were eggs, wheat and casein. We found reactions easy to read inasmuch as the skin of infants reacts very slightly to trauma from the scapel compared with the same amount of trauma on the skin of adult. Baby No. 40 showed a four plus reaction to egg protein which lasted thirty minutes. Baby No. 90 gave an unquestionable three plus reaction to egg protein. Both reactions proved positive on repeating the test. One of these cases had no history of atopy in the ancestors. A history could not be obtained concerning the antecedents of the other child inasmuch as little was known concerning the parents.

During embryonic life, food products, bacteria and antibodies from the blood of the mother enter the arterial system of the child with practically no change. This throws into the blood stream of the embryo food products of all sorts. Coca states that "an atopic individual, under adequate conditions of contact with the respective atopen, may be destined by heredity to begin to exhibit a particular clinical form of atopy (hay-fever or asthma, as the case may be) at a certain age of life, and that it may also be determined in the inheritance to which particular atopen, or group of atopens, the individual is to exhibit the hypersensitiveness." If heredity predetermines whether or not a child is to become sensitive, which is Coca's idea and appears to be true from our own findings and those of Cooke and Spain,[6] then during the embryonic life there is no reason why a child with inherent ability should not in some cases acquire a specific sensitivity to food protein or a non-nitrogenous product associated with the protein while in utero and therefore be born specifically sensitive. We believe the above explanation may answer the question of the pediatrician, "When did this child become sensitive?"

References:

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