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The Etiology of food sensitization in infants and children

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THE ETIOLOGY OF FOOD SENSITIZATION
IN
INFANTS AND CHILDREN

Raymond R. Rembolt

Senior Thesis
Presented to the College of Medicine,
University of Nebraska, Omaha.

1937
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INTRODUCTION

Interest in this subject was first aroused in the writer upon personal observation of a case of infantile eczema in which the etiological factor was obscure. A conspicuous lack of extensive work covering this phase of the subject was noted in the literature. Hence, it was determined to attempt to bring together the clinically important factors which are essentially concerned with the etiology of food sensitization in infants and children.

The term anaphylaxis was first created by Richet in 1902 (31). This he used in order to designate "the curious tendency that certain poisons possess of increasing instead of diminishing the sensitivity of the organism to their action." It was noted at this time that certain subjects reacted differently from the normal. Richet and Portier are the ones to whom credit is due for the working out of the principles of this subject by animal experimentation (31).

Since that time the scope of this subject has widened. In 1906 Rosenau and Anderson first demonstrated anaphylactic sensitization in the guinea pigs resulting from the introduction of horse serum into the digestive tract (60). This was later verified by numerous other workers not only in this country, but in others as well.

The application of this animal experimentation to human problems has been shown year after year with many satisfactory results. Many instances of this very thing will be seen in the dis-
cussion of this subject which follows. From these the great value of the animal procedures may be readily seen.

Clinical manifestations to demonstrate the existence of this phenomenon have been as plentiful as animal experiments. Certain of these symptoms, especially frequent in young infants have quite definitely proven this on the basis of alimentary sensitization. The abrupt onset of symptoms following ingestion of certain foods, the increasing intolerance of certain infants to cow's milk, the marked weight loss some of these same infants suffered when, after having been put back to the breast, cow's milk was taken again - all these facts which had previously been explained by the word "idiosyncrasies" had many characteristics common to those of experimental anaphylaxis (31).

Food sensitization, therefore, is well recognized in the clinical and laboratory fields. "Its role in pathology is extensive. Its biological role is far-reaching (31)." So, with the rapid unfolding of this subject and due to the fact that its possibilities are as yet far from being exhausted, the anticipation of future enlightenment is great. This latter may well be imagined when the tremendous list of varied manifestations of sensitization in different individuals is considered.

Strictly speaking, under the subject of food sensitization are included all of the reactions arising from a second ingestion of wholesome and normally well tolerated foods which, when first ingested, gave mild or no reactions whatsoever (31). As will be seen
in the following consideration, often the time of this first ingestion may be indefinite and the appearance of the condition results after what apparently seems to be the first ingestion of that food. This is especially true in those cases in which a congenital factor is involved.

It is not assumed that this thesis is an exhaustive study of the subject. Nevertheless, it shall be the writer's purpose to attempt to present the most important etiological problems as related to food sensitization in infants and children. Furthermore, it is acknowledged that with the ever increasing experimental work along this line, the balance of data that shall later be revealed may strongly favor some of the ideas which at the time of this writing lack support.
INCIDENCE

To determine the incidence of protein sensitization in the normal child (one having no clinical signs of sensitization) a study of the cutaneous reactions was made (6). Results obtained showed occurrence of sensitization in this group to be almost a negligible factor. Such a study makes comparison with other groups having clinical signs more meaningful.

a. Age

Such a study of age incidence has been observed by many workers. However, due to the fact that the same manifestations of sensitization in different patients may result from different sources, e.g., food, drugs, inhalation, etc., determinations are difficult. Hence, some of these studies are confined to age incidence in cases of certain manifestations.

In general it seems to be agreed that the greatest percentage of food sensitization occurs early in life. One writer states that by far the greatest percentage of food cases is encountered in the second year and then falls rapidly until by the sixth year it is one-fourth that of the second. He considers the occurrence unimportant after the sixth year (76).

The effect of the hereditary factor on the age of onset of sensitization is quite marked. Viewed as a whole, the more complete the familial factor the earlier the onset of clinical symptoms (73). This was recognized in 1916 when Cooke and Vander Veer
reported that of forty-four cases with a bilateral family history of sensitization, the greatest occurrence of clinical symptoms was between ages one and five years; of two hundred three with a unilaterial family history, greatest between ten and fifteen years; of two hundred fifty-three with no family history, greatest after twenty (20). More recently this same general conclusion has been reached by others (8)(13)(1)(73)(7)(27).

As shown by Balyeat (8), in certain cases food sensitization may be present at birth. He reports three cases where newborns developed symptoms on the first day, also cases of strongly positive skin reactions to intracutaneous food protein tests in newborns one to three days old. In such cases the first contact with the offending food protein would supposedly result in symptoms.

In studies confined to eczema with specific food sensitization as its cause, similar results as to the age of onset have been obtained. One writer finding the highest percentage of positive skin tests in the second six months of life states that in many cases the hypersensitivity to foods is acquired when the foods are first eaten (40). Other observers noted an increase in manifestations in partially and entirely breast fed infants up to the sixth month followed by a rapid decrease through the ninth month (27).

A study of fifty-six patients with asthma due to food sensitization were shown to present the largest number of reactions with age of onset between two and six years. Eighty-nine per cent of all cases of asthma due to food sensitization were seen to have
their onset between one and six years (44).

b. Sex

It would seem that male and female would be affected by food hypersensitiveness alike. This is confirmed by several different workers (7)(13)(40). However, Bray believes that males show clinical signs more frequently than females before puberty and vice versa after puberty (13). This latter is not confirmed or refuted by others.

c. Season

A work embodying twenty thousand sixty-one babies over a five-year period studying the effect of breast and artificial feedings on infantile eczema was made. In this it was observed that all groups of manifestations were increased in winter and spring and decreased in the summer and autumn (27). No attempt at explanation of this was offered.

d. Station

Balyeat states that food sensitization has no predilection for any one group, but that it affects the children of the rich and poor alike (7).

Thus, it seems evident that in general the greatest occurrence of food sensitization in children seems to be early, gradually decreasing throughout childhood in many cases. The family history of allergic manifestations has a definite effect
on the age of occurrence in the offspring. Manifestations seem to be greater in winter and spring.
PREDISPOSING FACTORS

Observations on predisposing factors seeming to have some effect on the occurrence of food sensitization in children seem to divide themselves into two groups. The first of these are of a general character and the second are those specifically related to the digestive tract, especially to the function of absorption. However, the fact that the two are closely related, the general factors effecting the absorptive function, is conceded.

a. General

A theoretical "balanced allergic state" or an "allergic equilibrium" is suggested by Balyeat (7). He proposes that signs of sensitization appear only when this equilibrium is upset. This unbalancing being caused by various factors, e.g., constipation, over-ingestion of the specific protein, upon addition of other sensitizing proteins, etc. This idea is speculative and, as will be shown in later sections of this paper, is hardly tenable in many cases.

Over feeding is an important factor in all ages. Infections, especially common colds, depress the digestive powers and predispose to the sensitization phenomenon (23). Hurried eating and poor mastication may be of importance in a few instances, probably more so in older children. This latter may possibly be of significance with the loss of the decidual teeth or in cases of infected and sore gums where they are too painful to allow proper chewing. Nervousness, although an important factor due to its
interference with normal digestion in the adult, is probably of less significance in children except in a few cases. Hypochlorhydria, a potent cause of inadequate gastric digestion, may be of importance in a few cases (14). (Further discussion of this last factor appears later).

French observers have likewise observed the importance of overfeeding as a predisposing factor to food allergy in children (31), recognizing that infants and children are frequently subjected to this. Other important factors which they believe present and which predispose to entrance of foreign proteins into the bloodstream are the feeble activity of digestive juices and the frequency of enteritis. Discussion of these appears in the next section.

b. Gastro-intestinal Absorption

It has been shown that under various conditions the gastro-intestinal absorption in children differs from that in the normal. An attempt will be made to present some of this data. Hence, consideration of these separate conditions and the effect of other factors on the absorption from the digestive tract will be taken up individually.

1. In the newborn infant:

Considerable differences of opinion exist regarding the passage of antigenic protein through the wall of the alimentary canal in the newborn. Those favoring the passage present evidence which seems to be conclusive (84)(67)(53)(3)(26) while those ad-
verse to the idea cite work which seems equally convincing (4)(64) (66)(35). An example of the former is well demonstrated by the work of Grulee and Bonar (26).

They used as their subjects an unselected group of infants. To these a two per cent solution of egg white was given between nursings instead of water. Morning urine specimens were collected daily and precipitin reactions carried out using an anti-eggwhite rabbit serum to determine the presence of the antigen. They found their first positive reactions in urine of infants who were in their fourth day of life. In the period from the fourth to the eleventh day there was approximately the same proportion of positive reactions for each day. No reactions were obtained in infants after the eleventh day, although they acknowledge the fact that there was an insufficient number of cases to make this latter observation of great significance. They conclude that the intestinal wall of the newborn infant is permeable to small quantities of egg white, demonstrated by precipitin reaction in the urine from the fourth to the tenth day. This they consider to be not a reaction of specific cases, but a general characteristic of that period of life. Others have made similar conclusions from blood studies (84).

Schloss comments on the "discordant results" in this type of investigation in his review of the literature (64). He is of the opinion that in much of the work in which positive results have been obtained, relatively large amounts of the antigen have
been given. He further states that this does not prove the
general principle that the intestine of the newborn is regularly
permeable to heterologous protein ingested in physiological amounts.

2. In the normal infant:

Evidence in these cases tends to favor physiological
absorption of antigenic protein \((84)(67)(53)(4)(3)(64)\). These
observations have all been made by means of precipitin tests on
the blood following ingestion of the protein for the first time with
the exception of one work \((84)\) in which the conclusions were based
on skin tests. In this latter, intracutaneous injections of serum
from a patient highly sensitive to egg were made in normal infants.
Following egg white ingestion these sites were observed for re-
actions. Positive reactions, interpreted as indicating presence of
the antigen in the blood were found in seventy-two and five tenths
per cent of the cases.

It is generally agreed by most observers that in these
normal infants the precipitin in the blood appears promptly.
Furthermore, the degree of precipitin formation is slight. And,
lastly, it is demonstrated for a comparatively short period \((4)\).

3. In infants with diarrhea:

It was early observed that infants with diarrhea had an
abnormal absorption of antigenic protein from the gastro-enteric
tract. Two Italian workers were some of the first to note this \((35)\).
Their work consisted of testing the patient's blood for casein using
rabbit serum which had casein precipitating properties. They obtained positive results uniformly with serum from bottle-fed babies showing symptoms of gastro-intestinal disturbances on cow's milk. Positive results also occurred in the blood of sick newborn babies given a little cow's milk. Negative results were obtained in normal healthy infants at any age.

A year later similar results were obtained by means of the precipitin reaction on the urine of infants given antigen by other workers. That is, negative reactions were obtained in the normal indicating that the intestinal tract is usually impermeable to undigested foreign protein and positive reactions obtained in those with gastro-enteric disorders indicating absorption of the protein in an undigested or partially digested state (66).

An interesting study of thirty-three cases of infants with moderate and severe diarrhea was made by Schloss (64). Antigen was demonstrated in the blood in seventeen of these. However, precipitin appeared in the blood of most of those who failed to show antigen within ten to fourteen days later. He believes, due to reasons which will not be discussed here, that the precipitin reaction is the most reliable means of determining the passage of the undigested antigen through the enteric canal. He concludes that the absorption of this undigested protein may be a prominent factor in causing toxic symptoms during infantile diarrhea.

In contrasting the absorption of protein in the normal with that in the infants with diarrhea, certain differences which
seem to be of importance in the etiology of food sensitization are noted. In the latter cases, more protein is absorbed, absorption is of longer duration, and the precipitin appears much later and persists longer - indicating longer continued absorption of antigenic protein (3)(64).

4. In infants with marasmus:

It has been shown by methods similar to those described above that patients with nutritional disturbances, marasmus, absorb foreign protein in an undigested or partially digested state (66)(3) (64). The contrast between absorption in the normal and in these infants is similar to that of infants with diarrhea, viz., the latter show a greater protein absorption over a longer period of time and with a later appearance of the precipitin (4)(3). It is assumed that this phenomenon in these cases does have a deleterious effect, but just how large a part is played is not determined (64).

5. Factors influencing:

Inadequate protein digestion is thought to be of importance in this respect in some cases. This has been noted to be a striking common feature in cases of eczema (36). There is little in favor of the view that this is due to a deficient gastric acidity since observations by Rowley have showed the pH of gastric juice to be the same in those absorbing and those not absorbing antigenic protein (64). Some convincing results have been presented, however, to show that this may be due to a deficient enzyme action (14)(64)(3)(31). In
summarizing the consideration on inadequate protein digestion, it is suggested that this factor may act in a quantitative way rather than as a sole determining factor and that the permeability of the intestinal wall must be a constant influence.

Thus, increased intestinal permeability may be a prominent feature in other cases. Schloss considers impermeability developing after the first ingestion of a specific protein to be a specific definite reaction (64). This he has demonstrated not to be due to the action of digestive juices on the wall. Furthermore, this is an unknown mechanism and any attempt at explanation is only speculative (3). It is thought to be a factor of some significance.

In the event that these two above mentioned protective mechanisms fail to function, there still remain other factors, failure of which may lead to sensitization. The first of these is production of specific antibodies which may divert absorbed protein from body cells, thereby preventing its harmful effects (64)(53)(3).

Secondly, it has been shown experimentally by Claude Bernard, cited by Laroche and others (31) that the liver tends to act as a barrier to the passage of heterogenous proteins. Laroche, Fils, and Saint-Girons also state that in their experimental animals which were sensitized to food, they have "always" observed lesions of the liver (31). They go on to state that periportal sclerosis and fatty degeneration of the liver have also been observed by Barbier and Cleret (article not yet published) in several infants sensitized to cow's milk. Hence, in view of this work, liver insuf-
ficiency may be of some etiological importance in food sensitization in children. Lastly, the excretory function of the kidneys has been demonstrated to play an important role in removal of excess antigenic protein (53).

Thus, it has been shown that there seems to be no one predisposing factor which is applicable to all cases of food sensitization in children, but rather that there may be many. It seems to be fairly well established that gastro-intestinal absorption of the specific protein upon its first ingestion by the infant is a normal process. This absorption in the normal differs from that in other conditions, however, in the rate and duration of absorption, and in the time and duration of appearance of specific precipitins in the blood. Factors influencing gastro-intestinal absorption are many.
THE CONGENITAL FACTORS

One of the most difficult factors to evaluate in a study of this kind is that of the role played by heredity (9). The matings are impossible to control. The generations are long and the families not large enough to feature all possible combinations. Records are inadequate and quite subject to inaccuracies. Artificial sensitization is not easy even in individuals with abnormal capacity for sensitization. Some forms of sensitization may not be recognized due to the varieties of manifestations. The sensitization may exist in young children and not appear later in life. The types and causes are of great variety. The question of whether the transfer is definitely through the germ plasm or due to sensitization in utero is frequently difficult to determine.

Some explanation on this congenital basis seems to be necessary, however, to explain some of the interesting observations made by Balyeat (8). He made specific cutaneous protein tests on one hundred nineteen cases of newborns - most of the tests being made on the first three days after birth. Some of these he found to present a strong positive reaction, indicating that they were specifically sensitive at birth.

It has been argued that if a character is hereditary, the laws of heredity must hold in one hundred per cent of the cases (16). This is based on a study of eighty-four families. Of seventeen families in which one parent had asthma, one hundred two
children did not have asthma and eight did. Of thirty-six families in which neither parent had asthma, two hundred twenty-six children did not have asthma and forty-six did. In seven families with one parent hypersensitive to protein, thirty-six children were not sensitive and two were. Of twenty-four families without either parent hypersensitive, one hundred twenty-six children were not sensitive and twenty-eight were. Thus, it was concluded that asthma and "protein sensitivity" are not dependent on a true hereditary factor.

This idea is not supported by most observers, however, for the majority recognize a familial tendency as being quite well established. Not only has this tendency been demonstrated in a general way (17)(20)(61), but studies of specific forms of food allergy in children, e.g., eczema (39)(7)(40)(29), hay fever (73)(18), asthma (73)(18)(43), and others to be discussed later in this paper, substantiate this contention. One of the early observations embodying a total of seven hundred sixty cases and showing a marked familial disposition in sensitization of all forms being that of Cooke and Vander Veer in 1916 (20). In another instance a family of ninety-four persons extending through five generations was studied and showed a definite familial trend toward allergic manifestations throughout (71).

Although the family tendency toward food sensitization as well as other forms of allergic phenomenon is well established, the exact mode, whether germinal or on a placental permeability
basis is not so well understood.

a. Germinal Transmission

Controversy over this question is present as in many of the other factors considered. Difficulties in evaluation of ideas in this particular phase of the problem seem greater than in the phases to be discussed immediately following. Due to intricate problems of interpretation arising in this respect, it is not amazing that conclusive experimental data are lacking in the literature.

Balyeat (8) is quite firm in his belief that specific sensitivity is not inherited, but the ability to become so is inherited. This ability to develop individual specific sensitivity comes from the same germ plasm and the specific state results from any atopen with which one has adequate contact, according to him. He concludes that inheritance of sensitivity is a single Mendelian dominant, basing his conclusions on "evidence" obtained from case studies.

Another observer (16) is as firm in his belief that germinal transmission does not occur as is Balyeat that it does. The former states that protein sensitivity is not dependent on transmission through the germ plasm of a factor which is responsible for the condition in man. He believes that the sensitization factors are either present or absent. Furthermore, that no satisfactory evidence that characters resulting in a tendency for appearance of or a susceptibility for sensitivity exists.
It is quite evident that the only manner in which predisposition may come from the father is by germinal transmission of the character. In a study of several hundred cases of allergy (all forms) in children, a unilateral family history of allergy was found in fifty-one and five tenths per cent of the cases - occurring twice as frequently on the maternal side (13). Conclusions that germinal transmission is frequent in man were made from this study.

A compromise is derived by Bray (13) in commenting on the discrepancies existing between a study of one thousand eight hundred eighty-nine cases (73) and the theoretical results of transmission according to the Mendelian law. He considers one manner of inheritance to be on a chromosomal basis - males and females as transmitters. The other possibility is assumed to be due to active sensitization in utero - this in cases where no positive family history exists. In the absence of more conclusive data this idea seems to be most tenable.

b. Placental Transmission

The German, Ascoli, in 1902, was the first to demonstrate the transfer of heterologous proteins by means of placental permeability. Pregnant rabbits were given varying amounts of heterologous protein either by feeding or by subcutaneous injections. The young were then extracted by Caesarian section at intervals varying from one hour to several days. The blood of each fetus and that of the
mothers was then obtained separately. Blood serum thus secured was tested by the antigen-precipitin reaction for protein which had been previously given the mother. In cases where the mother had received large doses of protein the maternal and fetal sera, both gave evidence of such. If the protein dosage was moderate or small, then fetal sera was generally negative (56).

The importance of such animal experimentation in the study of the human problem becomes evident when a histological study of the placenta of different species is considered (56). It has been shown that the placenta of man, guinea pigs, and rabbits, is permeable to antitoxins, precipitins, bacteriolysins, heterologous proteins, protein sensitizing antibodies, etc. The placenta of cows, goats and sheep is not permeable to these same substances. The explanation of this lies in the fact that in man and rodentia there is a single cell membrane separating the maternal from fetal circulation and in ruminants there are three cell layers separating these circulations. Hence, under certain conditions the passage of heterologus substances thru the placenta is a physiologic function and not a pathologic one in man.

Although these findings were not confirmed by one study of only ten selected cases of hay fever and asthma in pregnant women, they are substantiated by many other works (8)(46)(1) and clinical evidence to be offered following.

1. Active sensitization in utero:

Active sensitization is brought about by the direct influ-
ence of the sensitizing agent transmitted through the placenta of
the mother to the cells of the fetus (13). It has been shown above
that the placenta of man is permeable to proteins in their unchanged
form. Thus, it may be assumed that excessive indulgence in certain
foods on the part of the mother after conception and before partu-
rition might result in active sensitization in the fetus - manifes-
tation of such appearing with first contact of the newborn with the
offending protein.

Animal experimentation to prove this assumption has been
demonstrated. In one study in which guinea pigs were used, the
mothers were given sensitizing doses of horse serum intravenously
(54). Active sensitization to horse serum in some of the offspring
occurred - thus indicating passage of the antigen from mother to
fetus. Due to the close mother-fetus relationship between the
guinea pig and the human being, this is offered as evidence in sup-
port of the hypothesis that certain infants manifesting an allergic
state upon first contact with a foreign protein have been sensi-
tized in the uterus of the mother and are thus prepared for this
manifestation after birth. In another study differing only in the
fact that the mothers were fed horse serum instead of receiving it
per injection, similar results were obtained (48).

Not only does animal study tend to verify the above suppo-
sition, but so does clinical observation (46). Following is one of
the cited case reports which is a typical example of many presented.
Case report: D.G. aged six months was first seen at the age of eight
weeks at which time she had eczema of both cheeks and seborrhea of
the scalp. She had been on breast milk and a supplementary simple
milk formula for seven weeks previously. She developed eczema and
vomited when the formula was first given and at each subsequent
feeding. The antepartum history revealed that the mother took two
to three quarts of milk and three to four eggs each day during her
pregnancy. Protein skin tests on the child gave positive reactions
to lactalbumin and whole milk. Under treatment consisting es-
sentially of using a denaturized milk formula instead of whole milk,
no vomiting occurred with feedings and the eczema had completely
disappeared by the end of the fourth month.

Hence, it seems well established that under certain condi-
tions an infant with a predisposition for allergy may become actively
sensitized in utero because of the mother's overindulgence in certain
protein foods during her antepartum period and after birth when
coming in contact with this food for the first time protein foods dur-
ing her antepartum period and after birth when coming in contact with
this food for the first time will manifest some form of allergic
phenomenon (37).

2. Passive sensitization in utero:

Passive sensitization is produced by passive transfer of
antibodies from the sensitized mother - both mother and child show-
ing the same sensitization (13). This has been shown not to be of
common occurrence in man (20)(13)(49). The short duration of such
sensitization in the offspring and failure of passage of the same to the third generation is well established (55)(52)(20)(83)(49).

This latter is nicely demonstrated by studies of two families of guinea pigs in which sensitization was transmitted to the second generation, but no farther (52). In one family of this work the mother (P) was injected with a large dose of horse serum four days before parturition. One of the offspring (F-1-a) of the litter from this mother (P) died of anaphylactic shock when given a shock injection of the serum on its one hundred and ninth day - this tending to show that active sensitization in utero had occurred. A second member (F-1-b) of the same litter gave birth to two offspring (F-2-a and F-2-b) on its one hundred and fortieth day. Three days later the mother (F-1-b) died in anaphylactic shock following horse serum injection - showing persistence of the active state of sensitization up to the one hundred and forty-third day. One of the offspring (F-2-a) died on its third day following injection of horse serum, indicating a passive state of sensitization. The other offspring (F-2-b) gave birth to a litter on its one hundred and twenty-sixth day, none of which showed any reaction whatsoever when injected with horse serum - this showing a disappearance of the state. It is concluded that this same phenomenon may be present in humans and that active sensitization in utero persists longer than passive - the former through two generations.

To support this conclusion verifying its occurrence in the human, Ratner and Greenburgh have reported clinical evidence (49).
They report two cases of passive sensitization in utero, confirmed by passive sensitization in guinea pigs by means of serum. In subjectively commenting on their work, they are convinced that a highly sensitive allergic mother can sensitize the fetus in utero. They recognize the fact that it does not occur with as great a regularity as experimentally in guinea pigs. The same antibodies were demonstrated in the mother's and the child's blood by laboratory methods - very conclusive evidence supporting their contention.

Other workers have demonstrated the shorter duration of the passive sensitization in utero as compared with active (55). Guinea pig mothers were given intravenous horse serum before conception. Litter after litter of offspring from this same mother were observed. They were shown by anaphylactic death to be sensitive to horse serum from birth to an average of seventy-eight days after birth.

The importance of this mode of sensitization then is great in cases where the mother is highly sensitive or where allergy preponderates on the maternal side (49).

Thus, in spite of tremendous obstacles encountered in this phase of the study, the familial tendency to allergy seems well established in certain instances. Conclusive evidence regarding the germinal transmission is lacking, but the probability seems likely in some cases. Active sensitization in utero may occur. It seems to be of greater importance as an etiological factor of
food allergy in children due to its greater frequency in occurrence and longer duration than does passive sensitization. However, the latter may occur not infrequently.
THE ROLE OF BREAST MILK

One of the first observers to note that infants might show sensitization to breast milk was K. D. Blackfan working in the Department of Pediatrics at Johns Hopkins University (12). Of twenty-seven patients with eczema that he studied, twenty-two gave positive skin tests. He noted that these children reacted positively to egg white, cow's milk, and human milk most frequently. Several case reports are presented in which evidence of sensitization appeared when the newborns were being fed breast milk. Clinically the reactions cleared with the removal of the offending proteins from the diet. However, he made no attempt as to explanation of the mechanism regarding human breast milk whether the breast milk in itself was the source of the sensitization or whether it was some protein transmitted in the breast milk from the mother's diet.

Two years later, 1918, Talbot (18) made the first mention of the possibility of this transmission. He reports a case of an exclusively breast fed baby girl who developed a papular rash on her cheeks and body when three weeks old. The mother of the child had eaten about one pound of chocolate candy a short time previous to the appearance of the rash. Chocolate was omitted from the mother's diet and the eczema cleared. Cocoa taken by the mother two weeks later resulted in the reappearance of a similar papular rash. Omission of chocolate from the diet of the mother has resulted in no recurrence of the eruption. This he considers as
conclusive evidence that the foodstuff, in this case chocolate, may be transmitted through the mother's milk to cause reaction in the nursling in some cases.

A more extensive study of this problem was carried out by O'Keefe (39) at the Massachusetts General Hospital. Seventy cases of eczema as influenced by diet were observed. Cutaneous sensitivity tests were made for specific foodstuffs. In one exclusively breast fed infant he obtained a positive skin reaction to cow's milk casein. Upon restriction of the mother's diet to one pint of milk a day the baby's eczema improved. It disappeared following removal of cheese and cream in the mother's diet. Reappearance of the eczema occurred five months later when an attempt to wean the child, putting it on a cow's milk formula, was made. In other exclusively breast fed cases he found positive skin sensitivity to codfish and eggs respectively. In each instance the mother gave a history of a high content of these same foodstuffs in her diet. Likewise, in each instance the eczema improved or disappeared with removal of this food from the maternal diet. He concludes that foreign proteins may pass from the mother in breast milk in sufficient amounts to result in sensitization in the infant.

One of the most ardent supporters of this transmission of food proteins in human breast milk is Shannon (69). Not only did he observe clinical improvement in signs of sensitization among breast fed infants upon restriction of specific foods in
the mother's diet, but he also carried out animal experimentation to help prove his contentions. For a control he obtained breast milk from a mother whose child had shown clinical improvement in its signs of sensitization upon abstinence of egg in the maternal diet and who had eaten no eggs for a period of ten days. He injected this into each of three guinea pigs as a sensitizing dose. Two weeks later two of the pigs received intraperitoneal injections of egg white and egg yolk. The third pig was injected with a few drops of the same substance after the manner of Besredka (10). Nothing unusual occurred in any case, thus showing that the breast milk contained either no egg or an insufficient amount of egg to cause sensitization in the guinea pigs.

In a second experiment human breast milk was obtained at noon on three successive days that the mother had eaten two eggs for breakfast. A portion of each sample was then injected into each of three other guinea pigs as a sensitizing dose and a portion of the last sample saved for later experimental work. Twelve days later two of the pigs received intraperitoneal injection of a mixture of egg white and egg yolk while the third received a few drops of the same mixture per intrathecal injection. The pigs receiving intraperitoneal injections showed only immediate signs of irritability while the third showed typical anaphylactic reaction with recovery in about a half hour.

A third experiment was similar with the exception that the mixture of egg white and yolk was used for the sensitization
and a portion of the breast milk saved from the second experiment used for the shock injection in three other guinea pigs. The two pigs receiving intraperitoneal injections showed moderate anaphylactic response while the one receiving the intrathecal injection showed a marked reaction dying seven hours later. Controls were negative.

These experiments and others undertaken by the same man seem to establish the belief that egg protein may be present in the breast milk after the ingestion of a moderate quantity of egg - at least by some nursing mothers. From clinical observations it seems to be conclusively demonstrated that sufficient protein may be present in the milk under these conditions to cause a disturbance in some nursing infants. It is also deemed probable that this may occur with almost any other food the mother may eat.

Other observers have demonstrated similar results, i.e., signs of sensitization in the nursing infants which disappeared or improved upon removal of egg (38)(68)(19)(25), cow's milk (38)(47), lactalbumin (47), veal (68), fish (19), vegetables (19), fruits (19), navy beans (34), corn (34), or almost any food the mother might eat (68)(19)(70), from the maternal diet. It is suggested that usually it is not just one food which offers the offending protein, but multiple (70). These have all been clinical observations.

One of the first to seriously question transmission of protein allergens through human breast milk was Stuart (75). Commenting on the work of Shannon (69) two years previously, he
emphasizes the small series of cases of Shannon's. He is also of
the belief that if a reaction occurs from intrathecal injection,
it should also be present from intravenous injection and be demon-
strated by direct action on the uterine strip after the method de-
scribed by Dale (22).

In one of Stuart's experiments, pigs sensitized to egg by
intraperitoneal injection were given shock doses of breast milk
from five of nine of the mothers whose breast fed infants were
clinically sensitive to egg. These shock doses were administered
three to sixteen weeks after the sensitizing doses were given.
Eleven of thirteen pigs showed absolutely no reaction and the other
two showed only shivering for the first one-half to two hours, but
no true anaphylaxis. Then, four egg sensitive pigs were given
intravenous milk to which minute amounts of egg white were added.
Each of these pigs showed typical convulsions - three of them dying.

Another of his experiments used guinea pigs which had
been sensitized to this same human breast milk by intraperitoneal
or subcutaneous injections. Shock doses of intravenous egg white
solution were given fourteen to thirty-three days later. Of twenty-
one pigs, sixteen showed no reaction whatsoever, while five showed
only milk toxic reactions, as the two described above.

Uterine muscle strips of virgin guinea pigs which had
previously been sensitized to egg white by intraperitoneal in-
jections were treated by dilutions of breast milk from six of the
mothers in another study. No contraction of the muscle was pro-
duced in any muscle strip by concentrations of test breast milk which did not produce reactions in the controls. In another procedure uterine muscle strips from virgin guinea pigs which had previously been sensitized with breast milk from the mothers was treated with test solutions of egg white in Ringer's solution. Not one strip showed reaction to the egg white solution.

He (75) concludes that protein may be present in human breast milk in infinitely small amounts, but due to the fact that only small traces are necessary to sensitize guinea pigs and whereas the amount present in the breast milk of these mothers was not sufficient to cause a reaction, infants must be extremely sensitive to be affected by the amounts received from this source. He adds that his results have failed to suggest breast milk as a medium for transmission of antigen. Recognizing the clinical observations of sensitization in the exclusively breast fed infants which improves upon dietary restriction in the maternal diet, he states that the true explanation has not been offered as yet and the problem needs further study.

Further experimental work by Donnally (25) has tended to support the idea of breast milk transmission of antigen. In this study serum (serum F) was obtained from a child suffering from eczema and showing marked hypersensitivity to egg. By injection of 0.1 cc. of this serum intracutaneously in a normal individual and then having him eat eggs some hours later, a reaction occurred at the site of the injection. Hence, egg protein was assumed to
be present in the blood at that time.

Lactating mothers were given similar intracutaneous injections of serum F previous to which time they had not eaten eggs for several days. After fasting for twelve to fifteen hours, they were given two raw eggs orally. When the reaction at the previously injected site was noted, this indicating the time of antigenic egg protein appearing in the milk if any, the breasts were pumped. After preparation of these specimens, injections of such were made into sensitized skin areas of normal, healthy women who had no history of any allergic manifestations. The sensitized areas had been previously sensitized by intracutaneous injections of this same serum F. In each of the recipients at least one reaction was greater than that of the control and in no case was the control reaction greater than the test.

This tends to strongly support in a clinical way the evidence of elimination in the breast milk of food proteins ingested by lactating mothers. Commenting on Stuart's inability to confirm Shannon's experiments and conclusions, he believes grave doubt must be cast upon the validity of the former. In addition, recognizing the minute amounts of antigen necessary to produce a positive skin reaction in this study and in comparison with the reactions obtained by control experiments in which the dilutions of egg white were known, he estimated that the concentration of egg white varied from one part in a million to one part in a billion in these specimens of breast milk.
A criticism to Donnally's work is that his controls gave reactions (72). This tends to indicate that despite purification of the test milk, it still contained impurities causing reactions.

Continuing similar work, though carrying it a bit further, not only was the nursing mother's arm injected with egg sensitive serum, but so was that of her newborn baby (72). On the fourth day following the injection the mother was given an egg rich diet and the mother's and baby's arms were observed every fifteen minutes following. Of forty-seven cases in two different series, each mother reacted with an erythema and wheal at the injection site within forty-five minutes to an hour. None of the infants, however, showed any reaction. This was interpreted to be conclusive evidence that breast milk fails to transmit sufficient antigens for demonstration of passive transfer to the average newborn infant. In this connection it may be argued that those infants showing clinical sensitization are in a group entirely different from those which were observed in the above cited work. This was brought out in the section on the study of gastro-intestinal permeability appearing previously in this paper.

A Canadian has likewise favored the idea of transmission of antigenic protein in human breast milk (17). He noted in a study of seventy-seven children with symptoms of protein sensitization, that breast fed infants improved with the removal of offending proteins from the maternal diet. Another study of forty-one exclusively breast fed infants having eczema showed that sixty
per cent had protein sensitization (36). Of these, forty per
cent were cured and twenty per cent were improved by the results
of restriction of the maternal diet to proteins to which the
infants were demonstrated to be sensitive. Seventeen per cent
showed no improvement in a month and one-half, while the others
were not observed satisfactorily enough to make proper deductions.

From consideration of these works and others (44)(34), it
seems evident that clinical sensitization from antigenic transmission
in human breast milk is demonstrable to support Shannon's work (37).
Whether this is sufficient to explain some of the "unusual cases"
described by certain French allergists (31) in which a child could
not tolerate the milk of one nurse, but gains on that of another
is not known. No attempt to offer explanation of this has thus far
been made.

O'Keefe has observed that not one in forty-one cases of
eczema in exclusively breast fed infants showed sensitization to the
human milk protein. Of this same group, however, protein sensitiz-
ation was found in sixty per cent. This tends to show that in most
cases of food sensitization from breast milk, the antigenic protein
is transmitted from the mother through this medium and is not a
constituent part of the milk (36).

Little has been reported in the literature on the trans-
mission of protein hypersensitivity through colostrum. It has been
shown that its role in the transmission of immunity from mother to
her offspring in the human species is negligible. From this and un-
successful attempts at sensitization of guinea pigs by means of colostrum, it is concluded that this is of no etiological importance as regards food sensitization in children (57).

Thus, since it has been shown that the gastro-intestinal tract is permeable to unaltered proteins, the likelihood of sensitization of children by means of transmission of protein in breast milk is at least a remote possibility. And an infant already hypersensitive to some food may receive sufficient amounts of specific antigen by way of breast milk to cause clinical sensitization (1).
OTHER ALLERGENS

It has been stated that all foods except water and sugar may produce food allergy (31). Human breast milk as an allergenic factor in food sensitivity has been discussed separately due to its important role as such. Consideration of some of these other allergens which in many cases may be of as great import as human breast milk will now be made. It is recognized by a number of observers (6)(7)(36)(40)(44)(31) that of these antigenic food proteins eggs, milk, and wheat are the most common offenders in infants and children.

a. Eggs

Laroche, Fils, and Saint-Giron have made interesting and helpful studies of this food (31). They have found that raw, half cooked (eggs in the shell), or poached eggs are much more toxic than cooked eggs (hard boiled in particular). They note that both the egg white and yolk are capable of precipitating reactions, but that in some cases sensitization is dissociated. Furthermore, they conclude that eggs mixed in flour, as in pastry, tarts, dry cakes, etc., are frequently better tolerated.

A case study of severe idiosyncrasy to egg, the sensitizing dose seemingly coming at a time of gastro-intestinal upset (see previous discussion of predisposing factors, especially the section on gastro-intestinal absorption), is reported (62). Case Report: A male child, first seen at the age of eight years, was breast fed
without supplementary feedings for the first eighteen months. Seborrheic eczema of the face, head, and limbs first began at three months. He had severe coryza at nine months. During the first three years, beginning in the eighteenth month, he had a number of generalized convulsions. Respiratory infections were frequent. He was first given egg at ten days. At the time egg was first given he was suffering from diarrhea and no signs of sensitization followed its ingestion. When fourteen months old, he was given egg for the second time. Definite signs of intolerance, e.g., inflammation of the buccal surfaces and urticaria around the mouth developed immediately following the second ingestion. At the end of the second year an urticarial rash of the hands was noted when he was playing with eggs and egg shells. He showed repeated intolerance when given only minute amounts of egg even in frosting. Skin tests gave strongly positive reactions not only to egg, but also to chicken, duck, turkey and goose.

Demonstration of the absorption of unaltered egg protein from the gastro-intestinal tract has been made (77). Likewise, methods for measuring the presence and duration of unaltered protein in the circulation following ingestion of eggs have been offered (82). Results in this respect are similar to those discussed in a previous section on gastro-intestinal absorption of foreign protein in the normal and the abnormal, so further consideration will be omitted here.
b. Cow's milk

As will be shown at this time, the antigenic property of cow's milk is frequently seen and is an important factor. However, the principle behind it as an allergen differs from that demonstrated in human breast milk. It was shown in the previous consideration on breast milk that its anaphylactogenic properties were probably due to transmission of proteins from the mother's diet and not due to the milk protein itself. Evidence will be presented here to show that the opposite is true in the case of cow's milk.

Lyon demonstrated transmission of the proteins of white navy beans and corn through human breast milk following excess of the same in the maternal diet (34). He then attempted to demonstrate the same in the cow. By means of well controlled experimental work a cow was given a diet containing liberal amounts of these same proteins. He was unable to demonstrate these allergens in the cow's milk following the ingestion. This he interprets as evidence against the transmission of food allergens in cow's milk through its dietary.

Furthermore, chemically and biologically distinct proteins have been isolated from raw milk. The ingredients which are of considerable importance in food sensitization in children are primarily casein, lactalbumin, and lactoglobulin - these last two comprising the whey proteins (33)(51). It has been shown that sensitization to either or both the casein and whey fractions may result (31).
The effect of heat and acidification on the anaphylactogenic properties of these fractions is quite noteworthy. It has been shown by anaphylactic experimentation on animals that the allergic properties of the whey proteins are lessened even at a temperature of sixty degrees (33). This becomes progressively more marked as the temperature is increased. This same characteristic has been demonstrated by other workers (51)(21). On the contrary, the casein fraction is found to be quite heat stable, showing very little change in its anaphylactogenic properties even after evaporation (21)(33)(51).

It is not surprising then that a marked reduction in sensitizing ability resulting from evaporated, freshly boiled, and acidified evaporated milk when fed by mouth has been noted (51)(23). This is thought to be due primarily to the coagulation of the whey proteins. This coagulation is thought to delay the passage of proteins through the gastro-intestinal tract leading to a more complete digestion thus diminishing the probability of absorption of native antigens. It has also been suggested that in addition, the curds of the treated milks are smaller, hence they less frequently lead to sensitization (23).

In an early writing, Schloss reports observations on five infants who showed signs of sensitization when fed raw cow's milk, but who showed no reaction when given evaporated milk (63). He suggests the possibility that these may have had a sensitization to bacterial proteins in the raw milk. No further support to this
contention was encountered in the preparation of this paper. Hence, with no experimental verification, this as a factor is considered only as a remote possibility.

Talbot reports two cases which seem to be quite typical examples of sensitization to cow's milk (79). Case report No. 1: A healthy baby boy was given milk which was well tolerated for the first time when eight and one-half months old. Due to an otitis media he was not given milk again until three weeks later at which time immediate signs of sensitization accompanied the ingestion. Skin testing showed a strongly positive reaction to cow's milk protein. Case report No. 2: A malnourished child was given cow's milk formula for the first eight weeks of life. During this time he lost weight, had undigested stools, and failed to sleep well. He was then nourished by a wet nurse from his ninth week on. Attempts to give cow's milk since that time have all produced signs of sensitization in the child. Skin testing showed a positive reaction to cow's milk protein.

c. Wheat

The importance of this allergen in cases of food sensitization in children has been classed along with eggs and cow's milk (44)(7)(36)(31)(40). In a series of cases of asthma in children with food allergy as the etiological factor, wheat globulin was found to be the most frequent offender of all of the cereal grains. Occurrence of this sensitization is more frequently found in older
children rather than young infants. This is undoubtedly due to
the relatively late ingestion of this protein, thus tending to show
that hypersensitiveness to foods may be acquired when the foods are
eaten (40).

d. Miscellaneous

Fish, mollusks and crustaceans are not uncommonly en-
countered as allergens (59)(15)(31)(44). Due to the fact that they
fail to enter the young infant's diet, they are more often factors
in the older children. It is reported that the most toxic fish in
our country are the rayfish, mackerel, tuna fish, salmon, herring,
pike and smelts (31)(44). Of the mollusks, mussels are considered
to be the most anaphylactogenic and the most toxic. A remarkably
sensitizing toxin extracted from mussels is mytilo-congestine, which
is thought to account for this character (31).

Meats of all kinds may act as allergens. In a study of
asthma in children it was thought that the incidence was about the
same for all meats (44). Others are inclined to consider veal and
pork as somewhat more frequent offenders. Effect of cooking on the
sensitizing factors is considered negligible (31)(59).

The etiological importance of one of the cereal grains in
food allergy, viz., wheat, has been discussed above. Other members
of this group which are of slightly less significance in this re-
spect are barley, rice, rye, oats, corn and buckwheat (44)(40).
Sensitization to barley may appear early in life due to the fact
that many infants are given barley water when only a few days old (62). Upon addition of cereals to the infant's diet, the other members of this group play their part.

Nuts have been reported as causative factors in alimentary sensitization. Of these, one writer believes Brazil nuts to be the most frequent offender with almond and chestnut next in importance (44). Schloss cites a case of a child that showed definite signs of sensitization upon his first ingestion of almonds at six years of age (62).

Nearly all vegetables, especially radish, lettuce, and mustard (44), have been shown in occasional cases to cause signs of sensitivity following their ingestion (31).

In like manner fruits, with strawberries most frequently the allergen in this group, have been shown to be not uncommon incitants (31)(44).

Likewise, beverages with coffee playing the major role have been occasionally responsible as precipitating factors of manifestations due to food allergy (44).

Levin reports a case of allergic epilepsy in a three year old child (32). Skin testing showed a strong reaction to American cheese with a slightly less severe reaction to Swiss and Roquefort cheese. The child was placed on a cheese-free diet and had no attacks during this time. Upon ingestion of cheese nine weeks later, another epileptiform attack occurred. Since being placed on a strict dietary restriction of cheese, no further signs
of sensitization have occurred.

Not all of these cases show a single specific sensitization. Peshkin reports that one-eighth of his total series of food protein sensitive cases react to entire food groups (44). Similar observations have been made and reported by others (59) (62).

At the beginning of this section it was suggested that sugars have no anaphylactogenic properties. To confirm this idea conclusive evidence based on well controlled anaphylactic experiments on guinea pigs has been gathered by Ratner and Gruehl (50). They have shown corn syrups and pure dextrimaltose sugars to be non-anaphylactogenic. However, the addition of wheat germ or dried milk to these preparations converts them into substances which are definitely anaphylactogenic in character. They explain that those individuals who cannot tolerate honey may be sensitive to the specific protein elements of the nectar from which the honey is derived, e.g., buckwheat.

Thus, it appears that nearly any food substance with the exception of sugar and water may be of etiological importance as an allergen for sensitization in children. Of special importance in this respect are eggs, cow's milk, and wheat proteins. The effect of heat, acidification, and drying in diminishing the sensitizing properties of milk seems real.
SUMMARY

A study of the occurrence of protein sensitization, as evidenced by positive skin tests, was shown to be almost a negligible factor in the normal child. The hereditary effect on age incidence of food sensitization is quite real - in general, the more complete the familial factor is, the earlier the clinical onset. Male and female are affected alike. Manifestations of sensitization are more prone to occur in winter and spring. As regards station in life, there is no predilection for any one group.

There are a number of predisposing factors in the etiology of food sensitization which may be of some importance. Of the general factors, overfeeding, infections, hurried and poor mastication, nervousness, and possibly hypochlorhydria may be of significance. Gastro-intestinal absorption of protein upon its first ingestion is thought to occur in normal infants, but its occurrence in newborns is questioned. Absorption of antigenic protein in the infants with marasmus and diarrhea is shown to be of usual occurrence. This differs from the absorption in the normal, however, in that in the normal infant precipitin appears more promptly, the degree of formation of the same is slight, and it is demonstrated for a comparatively short time.

Several important factors which have an effect on the rate, amount, and duration of protein absorption from the digestive tract have been demonstrated. These include inadequate protein digestion, increased intestinal permeability, and impaired functioning of
certain protective mechanisms. Specific antibody production, proper liver function, and excretion by the kidneys are the factors leading to this important protection.

The existence of certain congenital factors cannot be denied. There is some evidence to favor the idea of germinal transmission in some cases. Sufficient conclusive evidence is not present in the literature to determine whether this is a transmission of a definite sensitive state or of a hypersusceptibility to protein sensitization.

Placental transmission of antigenic protein, antibodies, precipitins, etc., seems to be well established. Active sensitization has been shown to occur in humans by direct influence of the sensitizing agent transmitted through the maternal placenta to the cells of the fetus. This may follow excessive indulgence in certain foods by a mother after conception and before parturition. Passive sensitization in utero may occur in humans by passive transfer of antibodies from the sensitized mother to the fetus. Active sensitization is considered to be of greater etiological significance in food sensitization than passive.

In spite of the fact that some dispute exists regarding whether human breast milk is capable of transmitting antigenic protein from the maternal diet or not, the balance of evidence seems to favor the former. If so, the importance of this as an etiological agent in infants may well be imagined.

Almost any food with the exception of water and sugar
has been demonstrated as an allergen. Especially important in infants and children are eggs, cow's milk and wheat. The effect of heat, drying, and acidification in lessening the anaphylactogenic properties of cow's milk are well proven.
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