The Thompson-McFadden Commission, as quoted before, made the following statement in 1914. "Pellagra is, in all probability, a specific infectious disease, communicable from person to person by means at present unknown." The relation of this theory to the case under discussion, because of the following facts, has a special interest. For a number of years, there had been sent to the home of the patient, certain articles of fancy work and some fruit from Porto Rico. The fancy work had been done by Porto Rican women. One cannot but stop to speculate as to a possible connection between the theory last stated and these facts.

Only a few weeks before death was I certain I had to deal with a case of pellagra. My tardiness in recognizing the condition was because of my lack of the typical clinical picture. Here, as in many other cities, the recognition of one case of pellagra, assuring us of its presence, may stimulate study and lead to the discovery of many unrecognized cases. The fact that it had been reported in two cities as near as Taunton and Providence should have assured us of its presence here. Then it is said to be especially prevalent in southern mill towns, the character of whose industries and inhabitants is much like our own. Here, many of our foreign inhabitants come from pellagrous countries, all of which lends to the probability of many cases now existing among us unrecognized.

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ACID AUTOINTOXICATION IN INFANCY AND CHILDHOOD.*

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BETA-OXYBUTYRIC acid, diacetic acid and acetone may be grouped together under the col-

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lective name of the "acetone bodies." Their relation in the order of formation is probably beta-oxybutyric acid, diacetic acid and acetone. The acetone bodies are due to one common cause, that is, a peculiar inhibition of the oxidative processes. The failure of oxidation is not due to lack of oxygen, but to some local interference with oxidation. The excretion of beta-oxybutyric acid represents a much more advanced degree of oxidative perversion than the excretion of acetone or diacetic acid.

Origin of the Acetone Bodies. Beta-oxybutyric acid can be formed only from fats, by degradation, or by synthesis from bodies containing two or three carbon atoms. In the latter case it would be immaterial whether these bodies were a product of the disassimilation of albumen or of fat. It is a one-sided view to consider only the fats or only the proteins in this connection. The phenomenon of acetonuria with its many modifications is easily comprehensible if it is understood that acetone is a synthetic product derived from certain bodies which contain few carbon atoms and which may be derived from different sources. Normally the fragments of the proteins and fat molecules which contain but a few carbon atoms undergo further oxidation. This occurs, however, only in the presence of a sufficient quantity of carbohydrates. The explanation probably lies in the fact that the carbohydrates contain so much oxygen. A portion of this oxygen is presumably liberated when the carbohydrates are broken down and is used for the oxidation processes.

Acetone is normally present in the urine in small amounts. Diacetic acid and beta-oxybutyric acid are never present under normal conditions. The excretion of acetone is increased both in health and disease if the diet consists exclusively of meat and fat. This increase is not due simply to starvation, because the acetonuria persists even if the caloric value of the food is brought up to normal by the addition of fat. The addition of a small amount of carbohydrates under these conditions does not prevent the excretion of acetone in the urine. If, however, sufficient carbohydrates are added, the acetonuria ceases. The addition of fat to an ordinary diet does not cause acetonuria. The absence of carbohydrates is also necessary.

To sum up, the acetone bodies are formed from fat in the absence of carbohydrates or when the metabolism of the carbohydrates is abnormal. They may also, under certain conditions, be formed from protein, the amount formed from protein being, however, relatively unimportant in comparison with that formed from fat.

The acetone bodies are not formed in the digestive tract. This is proved by the fact that the administration of the acetone bodies by the mouth causes no symptoms.

Action of the Acetone Bodies. The deleterious effect of the acetone bodies is not due to any specific toxic properties which they possess,

but to their acid character in general and to the power which they possess as acids in withdrawing alkali from the organism. It must be clearly understood that the acetone bodies are in themselves not essentially toxic and that they can prove harmful to the body only by removing the bases. Under normal conditions there is a preponderance of bases over acids in the body. When acids are formed in, or introduced into, the body they have a deleterious influence upon it. The body has, however, a very efficient mechanism to guard against this deleterious action. The reaction of the body is regulated through the blood. Acids displace bicarbonate of soda from the blood and set carbon dioxide free. The excess of carbon dioxide is removed through the lungs. A neutral salt is left, which is removed by the kidneys. They excrete acid phosphate and save the base. The proteins, being amphoteric, are also able to neutralize a portion of the acid. Ammonia is also formed from the fixed proteins of the body and aids in the neutralization of acids.

Etiology of Acid Intoxication. In acid intoxication an accumulation of acids occurs as the result of the failure of elimination to keep pace with the production of acids. It may be due to an overwhelmingly rapid production of acids when the eliminating mechanism is normal, as in diabetes, or to the failure of the eliminating mechanism to dispose of a normal amount of acid, as in some cases of nephritis. In the latter instance the urine will contain little or no excess of the acetone bodies. When large amounts of an alkali are given when there is an acid intoxication from the overproduction of the acetone bodies, the elimination of these bodies in the urine may be increased from the setting free of the acetone bodies and the urine contain more of the acetone bodies, although the amount of the acetone bodies in the system is diminished. It is evident, therefore, that the amount of the acetone bodies in the urine does not necessarily show whether or not these bodies are accumulating in the organism.

Lactic acid, which can be formed from both carbohydrates and protein, may probably also be a cause of acid autointoxication. Evidence in favor of this assumption is that lactic acid is a constant constituent of the blood after exercise, and in dogs appears in the blood after the cramps produced by strychnine or phosphorous poisoning.

Acetone Bodies in the Urine. It has already been stated that under normal conditions the urine contains a minimum amount of acetone. This amount is so small, however, that it is not recognizable by the ordinary reagents. The acetone bodies appear in the urine within a short time after the cessation of the taking of food. The residual carbohydrates in the adult are used up after the fifth or sixth day, after which time the carbohydrates must be derived from the breaking down of proteins. The amount of carbohydrates which can be formed from the

metabolism of protein is relatively small and is not sufficient to prevent the abnormal metabolism of fat. The reserve of carbohydrates in infancy and early childhood is relatively smaller than in the adult. Therefore, the acetone bodies should appear more quickly in starvation in early than in adult life. I am not familiar with any data which show how soon after the withdrawal of food the acetone bodies may occur in the urine at this age, but from clinical experience I am inclined to believe that they rarely occur from this cause under forty-eight hours. It is probable that when there is an abnormal accumulation of fat in the parenchymatous organs, as is often the case in disturbances of nutrition in infancy, that the formation of the acetone bodies may occur earlier and be greater in amount.

Considerable quantities of acetone and diacetic acid are regularly found in the urine in a large number of diseases accompanied by high fever, both during the course of the disease and during convalescence. These bodies are especially common in the urine in pneumonia. Holt, for example, found that 70% of babies ill with lobar pneumonia showed acetoneuria. The acetone bodies are also very frequently found in diseases of the gastrointestinal tract, especially when there is a diminished ingestion of food and a disturbance of the digestion of the carbohydrates.

Few who have not examined the urine of children regularly for the presence of acetone and diacetic acid realize how frequently they are present. It is a routine procedure at the Children's Hospital, in Boston, to examine the urine for acetone and diacetic acid, as well as for albumin and sugar. They are found so often that no attention is paid to their presence, unless there are some symptoms of acid intoxication. Holt recently stated that acetone was found in 30% of the urines of 200 consecutive young children at the Babies' Hospital, in New York. A pediatrician in Boston told me the other day that acetone was found in 70% of all the urines which were brought to his office during the past year. It is evident, therefore, that the mere presence of the acetone bodies in the urine in children, while it denotes an abnormal condition of the metabolism, does not justify the assumption that the child is suffering from acid intoxication in the absence of other symptoms of this condition.

Diagnosis of Acid Intoxication. How, then, is acidosis, or acid intoxication, to be recognized? It must, of course, under ordinary clinical conditions be recognized by finding the acetone bodies in the urine. It must be remembered, however, that the mere presence of a small, or even of a considerable, amount of these bodies does not justify a positive diagnosis of acid intoxication. Better tests are the examination of the blood for the presence of abnormal acids, the determination of the amount of ammonia excreted in the urine and its relation to the total

nitrogen excretion, and the determination of the carbon dioxide coefficient in the expired air.

The most characteristic symptom of acid intoxication in infancy and childhood, outside of the presence of considerable amounts of the acetone bodies in the urine, is a peculiar type of dyspnea or, rather, hyperpnea, without cyanosis. The peculiarities of this type of respiration are that the rate of the respiration is increased, and that both inspiration and expiration are prolonged, the normal relation between the two being preserved. Another evidence of acid intoxication which is very frequent in infancy is a diminution in the output of urine, complete anuria being not at all uncommon. It is possible that in such instances the primary cause of the accumulation of acids is the disturbance of elimination through the kidneys. Vomiting is very common in acid intoxication in both infancy and childhood. There is, however, nothing characteristic about the vomiting in acid intoxication, and vomiting occurs in many other conditions. Vomiting, therefore, even when excessive, does not of itself justify a diagnosis of acid intoxication. Acid intoxication is not infrequently associated with diarrhea. There is, however, nothing characteristic about the diarrhea. In many instances of acid intoxication, moreover, the children are constipated. The breath not infrequently has a peculiar aromatic odor. This odor is, however, not always present and is decidedly difficult of recognition. The cheeks are often flushed and the lips of a peculiar cherry-red color. There is often, also, a white line about the mouth. None of these signs are, however, pathognomonic. It seems evident, therefore, that the recognition of acid intoxication is a much less simple matter than would appear from the statements of many physicians and of the newspapers.

Acid Intoxication in Recurrent Vomiting. It has been recognized for some years that certain cases of what is commonly known as recurrent, periodic, or cyclic vomiting are associated with the presence of the acetone bodies in the urine. In most of these instances it is probable that the acetone bodies are simply a manifestation of the inanition resulting from the vomiting and the consequent starvation. In others it is presumable that the symptoms are due to an acid intoxication. The reason for this presumption is that in certain instances the acetone bodies are found in large amounts in the urine at the very beginning of the symptoms, at a time when they could not possibly be due to inanition. Moreover, the symptoms cease with the disappearance of the acetone bodies.

Acid Intoxication in Diarrhea. The acetone bodies are also found not infrequently in the course of severe diarrheal conditions in infancy and early childhood. The majority of infants with severe diarrhea die, however, without any evidences of acid intoxication, either in the urine or symptomatically. On the other hand, a certain number of infants with severe diar-

rhoeas not only show large amounts of the acetone bodies in the urine, but show the typical hyperpnea and have a marked diminution in the output of urine. The majority of these babies die. In many of these instances, however, the symptoms of acid intoxication may be relieved by suitable treatment, but the babies die, after a lapse of twelve or twenty-four hours, without further symptoms of acid intoxication. It seems evident that in these cases the acid intoxication is a secondary manifestation and not the cause of the disease, although it may be in certain instances the cause of death.

Acid Intoxication in Infections. The acetone bodies are also found in large amounts in association with vomiting, with or without diarrhea, in infants and young children in the course of, or following, various infectious diseases. These diseases may of themselves not be serious. They are very likely to be relatively mild infections of the nasopharynx, tonsillitis, or "grippe." In these instances the symptoms of vomiting and prostration are entirely out of proportion to the severity of the original infection. When death occurs in these cases, it may be that it is due to acid intoxication. If so, it is evident, however, that the original cause of the disease is not acid intoxication and that the acid intoxication is due to some disturbance of the metabolism resulting from a toxemia or from a bacterial infection.

Epidemics of Acidosis. It is because of the occurrence within a short time of a number of cases of acid intoxication of this type, secondary to the infectious diseases, that we have heard so much in the past few years of epidemics of acidosis. It is evident, however, from what we know of the etiology of acidosis, that an epidemic of primary acidosis is an impossibility. When a series of cases of acid intoxication occurs, the explanation is simply that a number of cases of secondary acid intoxication have happened to occur in the course of an epidemic of some other disease. Much attention was attracted, two years ago, by a so-called epidemic of acid intoxication in Concord, N. H. This series of cases has been described by Metcalf. In 70% there was a well-defined infection of the respiratory tract or its adjacent cavities. In the others there was no suggestive etiologic point. A great deal has appeared in the newspapers during the past few weeks about an epidemic of acidosis in Boston and vicinity. I have seen a few of these cases in consultation and have known about a good many others. In the vast majority of these cases no examination of the urine was made. To the best of my knowledge and belief, no examination of the blood, of the ammonia content of the urine or of the carbon dioxide coefficient of the expired air was made in any case. In the vast majority of the cases, therefore, there was no scientific justification whatever for the diagnosis of acidosis. It is probable also that in the vast majority of instances the diagnosis of acidosis had no reason-

able clinical justification. In fact, it is probable that very few of the cases reported as acidosis had acidosis at all. How little basis there could have been for the diagnosis in many instances is evident when we consider, for example, that many of the so-called cases of acidosis occurred in the practice of a physician who, according to the newspapers, saw six hundred cases in his office and made nine hundred house visits in one week. If we stop to reckon how much time he could have given to each visit, it is evident that his examinations must have been very superficial and that the work in his laboratory must of necessity have been very limited. Further evidence of the general carelessness in diagnosis at this time is the fact that three cases were admitted to the Boston Children's Hospital on the same day with the diagnosis of acidosis. One of these children had pneumonia and another appendicitis. The third did have acetone in the urine, but was sitting up and crying for eggs the next morning.

It is true, nevertheless, that some very strange and unusual cases occurred during this period. It is also true that in a number of these cases large amounts of the acetone bodies were found in the urine and that, when these cases recovered, the acetone bodies first disappeared from the urine, while in the fatal cases they persisted. The histories of a few of these cases, which I myself saw are as follows:

CASE 1. A girl, of twenty months, vomited and had loose stools, Dec. 23. She was given bicarbonate of soda and did not vomit for the next two days, but continued to have four or five loose, greenish stools daily. During this time she took only a little barley water. She began to vomit again on the morning of December 26, and continued to vomit constantly from that time on. The movements from the bowels became very frequent and loose. It was impossible to tell how many she was having, however, because she was having treatment by seepage. She was seen at noon, Dec. 27.

She was conscious, but very feeble. She had evidently lost considerable weight. She was a little dusky. The heart was feeble and there were evidences of edema of the lungs. The abdomen was full, but otherwise negative. The liver and spleen were not palpable. There was nothing else abnormal. The urine had not been examined for the acetone bodies. The bicarbonate of soda which she was taking by mouth and rectum was continued and glucose was added to it. She died during the afternoon. There was no autopsy.

CASE 2. A boy, of 28 months, that had been perfectly well and had eaten nothing unusual, suddenly began to vomit at 5 p.m., Dec. 31. He continued to vomit about every fifteen minutes up to the time that he was seen by his physician, two hours later. He was then profoundly collapsed, pale and with cold extremities. The temperature in the groin was 96.4° F. He was given bicarbonate of soda by mouth, but this was vomited. When I saw him at 10.30 p.m. he had rallied a little. His color was good. There was no odor of acetone in the breath. He was conscious, but much prostrated. The phys-

ical examination was absolutely negative. He vomited a little watery mucus during the examination. The urine, which was obtained a few hours later, contained large amounts of the acetone bodies. Bicarbonate of soda and glucose were given by the mouth, but were not retained. He continued to vomit up to three o'clock the next morning. Castor oil and calomel, which had been given during the night, brought away several very large, foul movements about this time. The vomiting immediately ceased and he was apparently rapidly getting well. Twenty-four hours later, however, all the symptoms returned, and he died in a few hours. The autopsy showed a marked general acetone odor of the body. The tonsils were enlarged and contained numerous small foci of pus. The liver was fatty and the kidneys somewhat degenerated. There was marked edema and injection of the brain. Streptococci were found in the tonsils, brain and spinal fluid. They were not found in the other organs or in the blood. Staphylococci were also found.

CASE 3. A boy, nineteen months old, was a little out of sorts on Dec. 27. He seemed all right, however, on the 28th. He had a good stool the morning of the 29th as the result of castoria given the night before. He did not seem very well during the morning, and his physician was called at 2.30 in the afternoon. He prescribed bicarbonate of soda, which was given at once. He vomited about 3 p.m., but not again until 7.30 p.m., when he began to vomit every few minutes and to have loose, watery, foul stools. He was seen at 9.45 p.m. The physical examination was entirely negative. There was no aromatic odor to the breath. He vomited a large amount of watery material several times and had two large, watery stools, slightly brownish and with a very foul odor, during the examination. He continued to vomit and have watery movements throughout the night, and at 6 a.m. the next morning had a convulsion and died. The urine was not examined.

In this instance the symptoms were typical of those of cholera infantum, and at any other time no other diagnosis would have been considered.

CASE 4. A boy of thirteen months, perfectly well, except that he had had a slight cold for several days, began to vomit at 4.30 p.m., Dec. 30. He vomited three times. He was given castor oil at once and thoroughly cleaned out. He was given bicarbonate of soda during the night and repeated enemata of bicarbonate of soda. He was started at once on barley water, to which lactose was soon added. The next day he had many stools, which were not foul. His temperature was 104° F. in the morning, 106° F. in the afternoon and 103° F. at midnight. There was no recurrence of the vomiting. The treatment was continued. He was much better on the morning of Jan. 1, and rapidly recovered. His physical examination was always negative. His breath did not smell of acetone. The urine was not examined. There is no proof, therefore, that this child had an acid intoxication. Acid intoxication would probably not have been thought of at any other time. Nevertheless, he responded to the treatment which has seemed most effectual in this condition, that is, the

immediate emptying of the intestinal tract and the administration of alkalis and carbohydrates.

CASE 5. A girl, sixteen months old, was a little restless on Jan. 21. She began to vomit on the 22d and had two loose stools. Her physician was called on the 23d. He found a considerable amount of acetone in the urine, ordered bicarbonate of soda and carbohydrates by the mouth and gave enemata of bicarbonate of soda. She vomited several times during that day, her temperature gradually going up to 102.4° F. There was acetone in the urine the morning of the 24th. She was seen at 4 p.m. on the 24th. She had evidently lost much weight, her cheeks were flushed and her lips cherry red. Her respiration was rapid and deep. The physical examination was otherwise negative. She was given castor oil and put on barley water with dextri-maltose, while the bicarbonate of soda was continued. She promptly recovered.

Pathology. Little or nothing is known as to the pathological changes in this condition. Degenerative changes have been found in the parenchymatous organs, but nothing in any way pathognomonic. In two cases in which this diagnosis had been made, which were examined recently in Boston by Dr. Magrath, the bodies both had a marked acetone odor, the tonsils showed definite evidences of infection in both, the livers were fatty and the kidneys somewhat degenerated. There was marked edema of the brain in both instances. Streptococci were found in the tonsils, brains and cerebrospinal fluid in both. In one the staphylococcus aureus was also present. No bacteria were found in the other organs or in the blood in one case, and no cultures were made from the other organs in the other case.

Treatment. The cause of the symptoms in acid intoxication being the withdrawal of bases from the organism as the result of an excess of acids in the system, it is evident that the treatment indicated is the introduction of alkalis into the system to neutralize the acids in the body and in this way to prevent the further withdrawal of bases from the body and to allow the reaccumulation of the bases which have been abstracted from the body. The best alkali to use is the bicarbonate of soda. This may be given by the mouth, by the rectum, subcutaneously or intravenously. It is preferable to give it by the mouth if it can be retained. It is best given in water, but, if desired, the taste may be disguised by orange juice or grape juice. It is seldom wise to make the concentration of the solution stronger than 1:20. It is usually better to make it 1:30 or 1:60. Stronger solutions are almost certain of themselves to cause vomiting. The general feeling is that as much soda should be given as possible. It is very probable, however, that excessive amounts of soda may of themselves cause vomiting and diarrhea, and perhaps poisoning. I am very confident that in a considerable number of instances in which I have

been called in consultation to see cases of supposed "acidosis," the vomiting and diarrhea were the result of excessive doses of bicarbonate of soda and not symptoms of acid intoxication. In one instance of which I know, in which a baby of fourteen months received three ounces of dry bicarbonate of soda in twelve hours, the baby was collapsed and almost moribund, apparently as the result of the large amount of soda. Other alkalis may be used, but are, as a rule, not as satisfactory as bicarbonate of soda.

Bicarbonate of soda should also be given by the rectum. The solution may be stronger when it is given in this way. The solution is more often retained when it is given by seepage than by enema. Seepage is, in my experience, the more satisfactory method. The solution used for seepage should ordinarily not be stronger than 1:10. It is, of course, useless to attempt to give soda by rectum when there is diarrhea.

When bicarbonate of soda is given subcutaneously, a 2% solution should be used. When given intravenously, a 4% solution is strong enough. The amount to be given must depend, of course, on the age and size of the patient.

The acetone bodies being formed chiefly from fat in the absence of carbohydrates or when there is a disturbance of the carbohydrate metabolism, another indication is to administer an easily absorbable and utilizable carbohydrate. Such a carbohydrate is glucose or dextrose. This may be given by mouth or by rectum. It is usually advisable to give the soda, both by mouth and by rectum, in a 10% solution of dextrose. In urgent cases dextrose may be given intravenously in the strength of 2½% of dextrose in normal saline solution. Kahlbaum's is the only readily available pure dextrose. When the vomiting stops and the patients begin to improve, the carbohydrates may be added in the form of the cereal waters or jellies, to which one of the various maltose-dextrin mixtures or lactose may be added.

Practically, the usual treatment is the administration of a 5% or 10% solution of bicarbonate of soda in a 10% solution of dextrose freely, both by mouth and rectum. In my experience the immediate and thorough cleaning out of the intestinal tract has seemed to have more effect on the outcome in those cases of acid intoxication secondary to infections or to diseases of the intestinal tract than any other single procedure.

It must be remembered that this treatment is simply for the condition of acid intoxication, and that this condition is not a primary, but a secondary one. Therefore, even if the condition of acid intoxication is relieved, the original causative disease remains. The patient may die, therefore, even after the acid intoxication is cured.