The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. LXI, No. 20

CHICAGO, ILLINOIS

NOVEMBER 15, 1913

THE PROTEIN POISON AND ITS RELATION TO DISEASE *

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In 1903, Vaughan and Wheeler found that the cellular substance of the colon bacillus contains a highly active poison. This was obtained by extracting the dried, dead cells with a 2 per cent. solution of sodium hydroxid in absolute alcohol at 78 C. (172.4 F.). This poison was partially purified by repeated precipitation from alcoholic solution with either mercuric or cupric chlorid and removal of the base with hydrogen sulphid. This poison kills guinea-pigs when injected intravenously in doses of 0.5 mg. When given intra-abdominally this dose must be multiplied by 16 and when given subcutaneously by 32 in order to cause death.

Subsequently the same, or a closely related, poison was obtained from other pathogenic and from non-pathogenic bacteria, and then from vegetable and animal proteins. This work has been repeated and confirmed by others in this country and abroad. It is now known as "the protein poison" and is believed to be a constituent of every true protein whatever be its source. The purest proteins known, such as edestin from hemp-seed and zein from corn-meal yield this poison. It is not found in certain albuminoid substances, such as gelatin. It is found in Witte's and De Chapeau's peptones, but not in that of Defresne. Whether or not the latter is prepared from gelatin is not known.

The symptoms induced by this poison are quite characteristic and can be divided into three well-defined stages. The first is that of peripheral irritation and is marked in the guinea-pig by attempts to scratch every part of the body. In man it is shown by an urticarial rash which spreads from the point of injection and may extend to every part of the skin and invade the visible mucous surfaces. The second stage is one of partial paralysis with rapid and shallow breathing. The third stage is known as the convulsive, and begins in isolated clonic movements which become more frequent and general, finally involving all the muscles of the body and terminating, as a rule, in death. With fatal or nearly fatal doses there is a fall in temperature, which with fatal doses is progressive, and the temperature may fall in guinea-pigs to 85 F. before death. When recovery occurs, the first symptom of this is a return of the temperature toward the normal. In both man and experimental animals, recovery from a single non-fatal dose is speedy, and a complete return to the normal condition may result within a few hours.

Small doses of this poison administered subcutaneously cause fever, and a like effect can be induced with unbroken proteins. By changing the size of the dose and the intervals of administration it is possible to induce any and every known type of fever in experimental animals. One can induce an acute fever, terminating fatally, in a few hours. In this type the temperature can be carried to 107 F., which seems to be near the thermal death-point in these animals. Intermittent and remittent fevers are easily established and varied at the will of the experimenter. A prolonged fever extending through weeks and with a chart not distinguishable from one of typhoid may be established and carried to a fatal issue in rabbits. In fever of this kind there is the usual morning recession and the afternoon exacerbation so characteristic of typhoid. Furthermore, there is increased nitrogen elimination, and progressive emaciation is observed.

When proteins are taken into the alimentary canal and are acted on by the digestive juices the product becomes poisonous at about the peptone stage, and if the peptone formed in alimentary digestion should be absorbed into the circulation it would be highly injurious; but the digestive process proceeds and the peptone is broken up into harmless amino-acids, which are absorbed and synthesized into the proteins of our bodies.

When proteins find their way into the blood without being brought under the action of the digestive juices of the alimentary canal they must be digested in the blood and tissues, and in this process the protein poison is set free and, since general distribution cannot be hindered, it exerts its deleterious effects on the body.

We now know that the symptoms of many diseases are due to the parenteral digestion of proteins. Whenever a foreign protein, be it particulate or in solution, alive or dead, gets into the blood and tissue it must be disposed of by parenteral digestion. There seems to be no great differences in the amount of poison contained in the molecules of ordinary proteins, whether they be vegetable or animal, and, as has been said, the action of the poison is the same whatever the protein from which it has come. Dead protein contains just as much poison as living protein, but if the latter can grow and multiply in the body it increases the amount of its poison. Quite naturally most of the foreign proteins that find their way into the blood are living, such as bacteria and protozoa. Researches into the poisonous action of ordinary proteins, however, under the influence of the condition of sensitization, have demonstrated that living proteins are not absolutely essential to the development of certain diseases. If in any way proteins find access to the blood and tissues and the body becomes sensitized, then disease and death may result without bacteria or protozoa playing any part in the process. It has been shown quite conclusively that hay-fever and kindred

* Read in the Section on Diseases of Children of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.

disorders are due to sensitization to the pollen of diverse plants. Horse-asthma comes from the inhalation of hairs, and possibly of other proteins, from the horse carried through the air in other forms. The inhalation of peptone or other finely divided proteins may cause acute and subacute inflammation of the upper air-passages. Sensitization may result from the absorption of undigested or partly digested proteins from the alimentary tract. Whether or not the summer diarrheas of infancy ever originate in this way is a question to which a positive answer cannot yet be given. There are some good reasons for suspecting that the lowered vitality of the infant by excessive heat may lead to absorption of undigested proteins, and in this way cholera infantum and kindred diseases may be induced. We have not enough information on this matter at present, however, to enable us to speak positively, and I shall confine myself to a brief statement of the part played by the protein poison in the bacterial diseases. Recent studies in protein sensitization have quite materially modified our views concerning the nature and progress of the infectious diseases.

Bacteria have generally been regarded as unicellular plant organisms. This view is without just warrant. There is no proof that the bacterial cell contains cellulose. Indeed, all the evidence that we have concerning the chemistry of the bacterial cell is quite to the contrary. The bacteria which have been most thoroughly studied consist largely, if not wholly, of nucleoproteins or glyconucleoproteins, and are therefore more closely related to animal than to vegetable forms of life.

It has been assumed, furthermore, that the chemical structure of the bacterial cell is relatively simple. This has been shown not to be true. The molecules which make up the greater part of the proteins of the bacterial cell are quite as complicated as those that are found in the cells of our own bodies. These molecules contain at least two carbohydrates, one of which is attached to the nuclein group, while the position of the other has not been determined; but the weight of evidence is that it is a constituent of the protein part. Bacterial cell-substance yields the nuclein bases, and the greater part of it consists of protein, as is shown by its abundant yield of amino-acids, both mono and diamino. It will be seen from this that, although bacteria may be morphologically simple and without marked differentiation in structure, they are chemically quite complex and highly organized. This means that functionally they are quite on a par with the cells of the animal body with which the pathogenic bacteria so often compete.

The newer theory of how bacteria cause disease may be stated as follows: The cell is the morphologic unit of life, though not the physiologic unit. The latter is the protein molecule which lies in the cell and of which the cell is essentially composed. Bacteria are particulate proteins, and viruses capable of causing disease may be without form recognizable by us. The only essential and constant distinction between living and dead matter is that the former is never in a state of equilibrium; it is constantly absorbing and excreting; it feeds and eliminates; it is constantly trading in energy; it is labile, not stable. Every living cell must form ferments by which it splits up the pabulum on which it feeds. Whether a given bacterium is pathogenic to a given animal or not depends on two things. First, in order to be pathogenic it must be able to split up and feed on the proteins of the animal body; otherwise it cannot grow and multiply in that animal's body and consequently cannot harm it.

Secondly, the ferments of the cells of the animal's body must not be immediately, at least, destructive to the invading bacterium. When the ferments of the body-cells have this destructive action on the bacterium, the latter cannot be harmful to the former. These two things determine the pathogenicity or non-pathogenicity of a bacterium, and one or the other or both lie at the base of all bacterial susceptibility and immunity. The pathogenicity of a bacterium is not determined by its capability of forming a poison, because there is no protein without poisonous content. The ferments with which cells, be they bacterial or body cells, split up their pabulum or prepare their food are known as extracellular ferments. They diffuse from the cell into the surrounding medium, and exert a cleavage action on those food substances which they are capable of thus altering. Some are highly diffusible and may pass through a relatively large amount of pabulum, while others apparently act only on those substances that come into contact with the cell.

Of all the bacteria with which we have worked the *Bacillus prodigiosus* yields the largest amount of the protein poison, but this organism is not pathogenic to man or laboratory animals because it cannot grow and multiply in the animal body. On the other hand, the anthrax bacillus yields a relatively small amount of the protein poison, and yet it is one of the most infectious organisms because it can grow and multiply in the animal body.

The extracellular ferments are not the only ferments with which living cells are supplied. Many, probably all, living cells have intracellular ferments, which are non-diffusible and remain within the cell. The function of these is to take the food as prepared by the extracellular ferments and build it into the cell tissue. It will be seen that the extracellular ferment is destructive or analytic in its processes, while the intracellular ferment is constructive or synthetic.

The important lesson which we have learned from our studies of protein sensitization is that the nature and action of cell ferments may be, to some extent at least, modified at will. Cells can be trained or educated to pour out a special ferment to digest a specific body. This is the explanation of vaccination. The virus of small-pox is pathogenic to the unvaccinated, but is non-pathogenic to the man who has had the disease or has been vaccinated. The typhoid bacillus is no longer infectious to the man who has been properly vaccinated against this disease. Vaccination is secured by introducing into the body that protein which causes the disease, but in a condition so modified that it will no longer cause the disease, but will lead the body-cells to pour out a ferment which will destroy that specific protein when it is reintroduced. In vaccination for small-pox the protein has been modified by being passed through the cow. A vaccine for anthrax is obtained by growing the bacillus at a high temperature or in the presence of a weak germicide. The dead typhoid bacillus serves as a vaccine. When an individual has been protected by one of these vaccines and is exposed to the disease, the organism is destroyed so soon after admission to the body that it does no harm, and in this way immunity is secured by vaccination. It is easily understood that this form of immunity is not absolute, but is relative, and may be overcome by severe or prolonged exposure.

Vaccines are now used not only as preventive but also as curative agents. Much harm is being done by their indiscriminate and ignorant employment, but their

proper use is rational and scientific. They are of special value in local infections, and they operate by stimulating a wide area of body-cells to furnish a ferment which destroys the bacterium that is the cause of the local condition.

In the light of what has been learned from studies of the protein poison and protein sensitization let us see how the typhoid bacillus acts in inducing the disease. The bacillus finding its way into the body grows and multiplies. Its extracellular ferment acts on the proteins of man's body and prepares the food which is built into typhoid tissue by the intracellular ferments. The ferments of the body-cells are not capable of destroying the invading organism and during the period of incubation it multiplies greatly. During this time the man is not ill. It is not, therefore, the growth and multiplication of the bacillus in the man's body that directly causes the symptoms of typhoid fever, because at the time of its most active growth there is no fever or other symptom. During the period of incubation the bacillus furnishes the ferment, and the proteins of the man's body constitute the substrate. These proteins without much change are taken into the bacterial cells and built into typhoid bacterial tissue. The process is largely one of assimilation and construction, and no poison is liberated; consequently there is no fever or other symptom. After about ten days the period of incubation ceases and the disease is ushered in. The body-cells, under the influence of the foreign protein and for the purpose of its destruction, begin to pour out a new specific ferment. During the disease the body-cells furnish the ferment, and bacterial cells constitute the substrate, the process is destructive, the protein poison is liberated and fever with its concomitants result. The person may die as a result of the too rapid liberation of the poison, from a lesion due to the effects of the products of the parenteral digestion or from chronic poisoning.

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ABSTRACT OF DISCUSSION

DR. JOHN ZAHORSKY, St. Louis: It is refreshing to pediatricists to find that many American pediatricists and physicians have rather held to the original view that, after all, it is the protein that causes the death of the babies in summer diarrheas. Holt of New York has held the same view. There are certain forms of diarrhea in children that are not bacterial. I think that this is now generally recognized. The method by which this poison is produced, how it enters the blood and what circumstances produce it, is yet to be worked out. These diarrheas occur early in the summer. The condition is ordinarily called fermentative diarrhea. It is attributed to carbohydrate fermentation. While we have acute attacks of indigestion in the winter, due to acute indigestion of sugar, in the summer we have diarrheas which we cannot cure by giving the various treatments. The diarrhea is persistent, sometimes for weeks; that type of disease, the toxin of which is unknown, is probably not a direct infection, but undoubtedly depends on some poison, as suggested by Dr. Vaughan.

DR. MARY STRONG, Omaha: I want to speak from the clinical point of view. In Omaha the climate is abominable in summer. Some ten years ago a healthy, live baby was born under my service. I saw that baby when it was about three days old, and for no reason that we could discover it was almost comatose, with a temperature of over 104 F. I did not have laboratory methods convenient for use. I used common sense. I had the baby stripped and sponged with cold water; cold water was injected into its rectum, and we gave it all the cold water that it would swallow; the baby promptly recovered without any change of food. It was having moth-

er's milk, which was good. I know now why that baby recovered. Since then, every summer I have seen babies in Omaha dressed according to the directions of the Eastern doctors, with flannel next to the skin. My first treatment is to take off every scrap of flannel. I think that the nearer naked the baby is in hot weather the better. I saw a baby in my office last summer with a high fever and acute diarrhea, dressed according to Holt. It was not dressed that way when it left my office. It had on one necessary garment and a slip—and I told the mother to take that off when she reached home. The baby recovered. I believe that I know now why it recovered. I found out several years ago that clothes kill a great many babies in the summer time, particularly flannel. It makes them so warm that changes take place in the digestive juices.

DR. C. H. JOHNSON, Grand Rapids, Mich.: Finkelstein has reduced the mortality in his institution from 60 or 80 to 7 per cent. by cutting out sugar and salt in a large degree. He agrees with everything else that Dr. Vaughan says. Finkelstein says that the death-rate in diarrhea has not been reduced by the sterilization of milk. He believes that the disease is due to chemical changes.

DR. C. G. GRULEE, Chicago: It seems to me that there is another side to this proposition—the prime factor, the one thing necessary for such a theory to be realized—that this protein must be absorbed through a deranged gut. What causes the derangement? In answer to Dr. Johnson, I may say that Dr. Finkelstein's ideas have received a serious jolt in the last year. Bendix and Samelson have shown that the injection of sugar solutions made from freshly distilled water does not produce a rise in temperature when injected subcutaneously, while, if the distilled water used is old, a rise in temperature is produced. This, although not yet printed, has also been confirmed in Finkelstein's own clinic by a young Chicago physician, Dr. Grace Meigs, in regard to salts. This does not mean that we cannot produce a rise in temperature from the ingestion of salts or sugar by mouth. In fact, it has been shown definitely that those experiments are correct; that a certain amount of salt or sugar does cause a rise in temperature. The only way in which the seeming conflict of these two propositions can be explained is that the sodium salts or sugar, when given by mouth or rectum, causes a change which allows absorption of some product from the intestine and in that way produces a rise in temperature and symptoms. They have not determined the matter definitely, but have reason to believe that the product in the stale distilled water is not bacteria; but that does not make any difference, nor does it combat this theory of Dr. Vaughan's. It seems to me that, while there are many points that will have to be worked out, we may be on the right track in regard to the causation of summer diarrhea.

There is protein in the intestine other than casein, other than the protein ingested from food, which may be active in the mucus. This has not been accorded the place by pediatricists, which it perhaps deserves, as the source of putrefaction. This may cause a great deal of trouble. As we go further with Dr. Vaughan's idea, we may find that it is absorption of the mucus unchanged.

DR. LOUIS BURCKHARDT, Indianapolis: Dr. Vaughan stated that some food is harmless at one temperature and harmful at another. In our city we have a first-class milk-supply. Our milk commission has controlled it. We have taken sample tests in the laboratories, and the last three tests came back with a count of three hundred. In spite of that, the board of health proposes to demand pasteurization of the milk. I am much interested to hear Dr. Vaughan's idea about the advisability of compulsory pasteurization of milk which has been produced under all the precautions.

DR. H. W. CHENEY, Chicago: Dr. Vaughan did not suggest it, but I wish to ask if this protein poison he speaks of is not the same as that present in horse-serum given therapeutically, which causes death in animals in which it is sometimes used. From a clinical point of view we can agree that some of the cases of summer diarrhea are caused by protein poison, but we know that a large proportion must be caused in other ways,

because we can cure these patients feeding skimmed milk, a protein-rich food.

DR. GEORGE S. CATTERMOLLE, Boulder, Colo.: In Colorado we have few cases of summer diarrhea. I believe the reason for this is our low mean summer temperature. Our nights are cool. Probably for this reason we are free from the intestinal disorders in infants that are so common in hot climates. So-called "cholera infantum" is almost never seen in Colorado.

DR. T. C. McCLEAVE, Berkeley, Cal.: I understood Dr. Vaughan to say that all protein poisoning is the same, the symptomatology depending on the localization in the body. In the exanthematous diseases, in which specific manifestations appear so largely in one organ, the skin, how does he explain the occurrence of the different characteristic eruptions under his theory?

DR. VICTOR C. VAUGHAN, Ann Arbor, Mich.: It is evident that the presence of other constituents besides proteins in the food influences to a great extent the absorption of proteins from the intestines. This absorption is largely a question of osmosis. It is altogether probable that one dilution of sugar favors the passage of the protein into the blood, while another dilution would have the opposite effect.

I am glad that this question concerning scarlet fever was brought out. As I have stated, experimental fever can be induced in animals by the subcutaneous, intravenous and intra-abdominal injection of any kind of protein. These proteins have their predilection places in the body, where they accumulate. This is true of both living and dead proteins. The pneumococcus protein accumulates in the lungs; the typhoid protein in the mesenteric lymph-nodes and in the spleen, and the proteins which are concerned in the exanthematous diseases accumulate in the skin and submucous tissues. We have shown positively by experiments in the laboratory that white of egg injected into the circulation of a rabbit soon disappears from the blood. Later it may be found in various tissues. White of egg injected into a rabbit intravenously accumulates largely in the skin and in the walls of the intestines. It is also found in the kidneys. Not only does the foreign protein disappear from the blood and become diffused through the tissues, but it also carries with it an appreciable amount of the normal proteins of the blood. The symptoms of one disease differ from those of another largely on account of the organ in which the foreign protein is deposited and in which it is disrupted. The most skilful physician cannot distinguish by the symptoms alone between a meningitis caused by the meningococcus and one caused by the pneumococcus or a third caused by the typhoid bacillus. In all acute infectious diseases the poison formed is one and the same thing. It is the protein poison that kills in all these diseases.

The question has been asked concerning the pasteurization of milk. I should prefer to feed a baby on pure rather than on bad milk, on milk with a low bacterial count than on that with high bacterial count, even if the bacteria are not pathogenic. Bacteria, whether they are pathogenic or non-pathogenic, split up the proteins of milk and probably render them absorbable without complete digestion. The exact relation of cholera infantum and the other forms of summer diarrheas to anaphylaxis has not been made out with certainty. I am, however, of the opinion that the absorption of partly digested proteins has much to do with the summer diarrheas of infancy.

ACUTE ACID INTOXICATION IN CHILDREN *

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This paper contains nothing new; but because the subject receives scant discussion in current text-books, and periodical literature contains articles dealing rather with particular aspects of the matter, it may be of some value to make a general survey of our knowledge of that impor-

tant disorder occurring in children which, for want of a better term for the time being, we may still tentatively designate "acute acid intoxication."

Acid intoxication is an extremely common phenomenon in a variety of pathologic conditions, but in children, usually from 2 to 10 years old, we see very frequently a symptom-complex in which acidosis is a marked and constant characteristic. Attacks are commonly recurrent, and may come on suddenly or be preceded for a day or two by a prodromal period in which are observed listlessness, anorexia and coated tongue, and, quite strikingly, a bluish pallid ring around the mouth and beneath the eyes, with dusky cheeks. Headache may be complained of, and there is usually a coryza and injection of the conjunctivae, with a variable cough. Intense nervousness, even to marked meningismus, may be exhibited in the beginning, though always as the attack progresses, and frequently throughout, the child is apathetic and, in extreme cases, may even develop coma. In any but mild cases, the appearance of the child is indicative of serious illness. The face is pinched and pale, or often cyanotic, the eyes, at first bright, become sunken and dull, the lips are dry and cracked, the teeth covered with sordes, and the tongue dry and brown over the dorsum, with "strawberry" edges. The abdomen is retracted, and general wasting may be extreme. The skin is dry and harsh, often scaling after a severe attack.

The breath is foul, but the sweetish, fruity odor of acetone can always be detected, and frequently permeates the entire room in which the patient lies. There is always fever, the temperature rarely exceeding 102 or 103 F., but occasionally being very high. The pulse is soft, rapid and irregular, and the respirations sighing and irregular, often slow and deep, with marked "air hunger," both clinical and experimental evidence seeming to show that the acid poisons have a direct depressing effect on the vasomotor and respiratory centers.¹ I have seen two cases in which asthmatic manifestations were a prominent feature of the attacks.

There is no desire for food, and vomiting, except in the mildest cases, is always present, and often is extremely intractable. Large amounts of fluid may be vomited, and the rapid dehydration of the tissues occasions a most intense thirst, the child constantly pleading most piteously for water. The bowels may be constipated, or, less frequently, loose, with green or gray foul stools. The urine is scanty, and may contain albumin, casts and blood. In one case under my observation the child passed only a few ounces of dark-green, syrupy urine in twenty-four hours, which solidified on boiling.

Prostration, in severe cases, is always marked, and not infrequently a fatal termination seems imminent; but deaths from this cause are very rare. The duration of the attacks is from one or two to seven or eight days.

Diagnosis, when one is familiar with the condition, is usually not difficult. Acute digestive disorders may be excluded by the absence of a history of dietetic errors, and the persistence of the vomiting and other symptoms; acute appendicitis by the absence of pain, tenderness, and rigidity; disease of the brain or kidneys, or beginning meningitis, at first readily suspected, by the progress of the attack, and the early development of the characteristic urinary findings. That acidosis and vomiting are frequently observed at the onset of an acute infectious disease may sometimes mislead one, and seeing a child for the first time with an attack of the kind we are considering, I am in the habit of mentioning this to the parents, lest pneumonia or one of the exanthems

* Read in the Section on Diseases of Children of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.

1. Ehrman: Berl. klin. Wehnschr., 1913, 1, 40.