functioning entirely, then these patients are not all complete diabetics. The principal characteristics of these patients is a persistent, high blood sugar and a 4-plus urinary sugar finding in the morning. This accumulation of endogenous sugar cannot be prevented except by giving insulin through the night. However, this procedure is not recommended. Because of the accumulation of sugar overnight, these patients need their largest dose of insulin in the morning but only just enough to take care of their food at the other two meals. In this way, these patients can be kept at a fairly normal level throughout the day and part of evening. In severe instances of diabetes, some doctors recommend giving a moderate dose of insulin with a lunch at about 8 or 9 P. M. Since these patients never are sugar free in the morning, the best time to check up on them (both blood and urine tests) is between five and six in the evening—when the noon dose of insulin has exhausted its action and before the supper dose is given. At this time patients should be found nearly normal if the diet and insulin are well adjusted.

How can one recognize these cases?

The very severe case easily is recognized by the result of the 24-hour quantitative estimation of sugar where the output will be found to be greater than was the sugar intake in the diet. The moderately severe case, on the other hand, presents rather more difficulty. While his output of sugar is very large, it does not exceed his intake. One is unable to say immediately whether or not a part of this sugar has its source in an over-night endogenous production, or whether it represents simply unused food waste. If the day's insulin evenly is distributed in proportion to the meals, insulin reactions in the afternoon and evening probably will lead one to suspect the situation. By careful observation and the finding of abundant sugar in the morning specimens, both blood and urine, one soon may place him in the category to which he belongs.

The important and difficult requirements in both these types of patients is to get the insulin properly adjusted. The calculation of insulin dosage for the excess sugar in the blood always holds, for all cases alike; but in the above-mentioned types of patients the figure for the urine sugar—one unit of insulin for each gram of sugar—does not hold. In such circumstances it will take rather longer to adjust these patients. However, such instances are not numerous.

CONCLUSION

The above outlined method of establishing diet and insulin therapy in a diabetic is direct and has proved to be reliable. Since it is a purely mathematical procedure, it should produce the same happy results in the hands of the inexperienced and timid worker as it does in those of experienced doctor or specialist.

NOTE: It is interesting to observe the action of insulin on different individuals. This study of the variable action of insulin was the beginning or first step in working out the above method; but readily one may see that it is not necessary to do this on every individual. To omit it saves much time and expense. When individualized action studies are done they must be carried out on a separate day.

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Studies in Food Allergy* . . . A Preliminary Report

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THE whole subject of food allergy practically has developed into a big question mark. According to Vaughan and others, who have had large experience (1), skin tests are not more than 50 per cent reliable. This investigator states that of 200 positive skin tests to foods, only 100 of the foods actually were causing trouble. The other half were "false" positives, or at least, were not responsible for disturbances. For every 100 foods actually found to be factors influencing symptoms or signs by the skin-testing method, 40 additional foods were found to be inimical agents by the method of keeping food "diaries" or by "elimination" diets; yet these foods returned negative skin tests.

It is difficult for the authors to believe that any

*EDITORIAL NOTE: Inasmuch as both clinical and investigative aspects of food "allergy" are in a confused state and because progress along so-called orthodox lines appears to have reached an *impasse*, on the basis of its offering suggestions along different pathways, this article has been deemed worthy of publication. It is a "preliminary report". The data presented may find elaboration by those interested in the problems discussed. Be that as it may, such work, performed by men busy with everyday practice, warrants recognition.

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test which in the hands of experts admittedly is 50 per cent unreliable can be regarded in any special instance as a dependable specific procedure. Every doctor who has worked in the field of allergy has known patients who were sensitive by skin tests to certain foods at one sitting, and were negative to the same foods a week later. Plainly, the skin test does not have the same specific significance in food allergy as does an increased lipoid content of the serum in syphilis, upon which the sero-diagnosis of that infection depends.

Likewise, the leucopenic index (e. g., "Widal crisis") as an indication of allergy, according to Vaughan is only 67 per cent correct, and the method has the further disadvantage of being too time-consuming for routine use. Food "diary" and "elimination" diets look well on paper but in our hands they have proved impracticable. Just about the time one seems about to gain information by this method, the patient is called out of town, where he must eat at restaurants which breaks, unavoidably, the entire planned regimé.

It would seem that the reason why so much confusion has existed in the field of allergy is that, etiologically, there are different types of allergy just as there are different types of infection. Perhaps the underlying mechanism is different for each type. There is evidence that food sensitization essentially is a pancreatic disturbance, as we shall attempt to show, while allergy to pollens, bacteria and other allergens probably depends upon an entirely different mechanism. In this study we are concerned only with sensitization to foodstuffs. We believe that we have uncovered some very pertinent data.

It has been advanced that sensitization to foods is a form of anaphylaxia. In animals, only the injection of whole, soluble, undigested proteins will produce sensitization. Split products of digestion will not produce sensitization. It is believed that sensitization results from the formation of specific antibodies, and that it is the union of large amounts of antibody with its specific antigen which is the cause of the chemical "explosion" which we call anaphylaxia. Some workers claim to have demonstrated antibodies in the serum of sensitive animals but a greater number were unable to confirm these findings. Our impression derived from the literature is that antibodies never have been surely and definitely demonstrated. For a full exposition of our present knowledge the reader is referred to any of the standard texts on the subject, such as Vaughan (2), Tice (3) or Kolmer (4).

DISCUSSION OF METHODS AND RESULTS

Because antibodies are specific substances formed as a result of specific allergens gaining entrance to the blood stream, we have worked with allergens which were extracted from the various foodstuffs in the forms in which commonly they are eaten. Beef, for example, usually is taken in the cooked state, while apples are usually eaten in the raw state. We prepared beef antigen by extracting finely chopped beef with saline solution. The beef was cooked in the saline solution for two hours, after which the solution was filtered and neutralized for free acidity. Those foods which are commonly eaten in the uncooked state were extracted with cold saline for 24 hours, after which the saline was decanted, filtered and neutralized.

Allergens made in this manner were studied by means of Weichardt's epiphanin reaction (5). Weichardt found that if a solution containing soluble protein is introduced into a "system" composed of a balanced mixture of sulphuric acid and barium hydroxide, plus phenolphthalein as an indicator, the protein alters the surface tension of the finely divided barium sulphate particles by its colloidal action, so as to increase the absorption of H or OH ions, depending on whether or not the protein is fixed or free.

Weichardt's reaction is dependent upon physico-chemical properties of absorption and it acts in accordance with the following generalizations: (6) Solutions containing colloids (proteins) *i. e.*, antigen alone, serum alone, or antigen plus nonspecific serum, act in the epiphanin system by shifting the phenolphthalein endpoint in the sense of absorbing OH ions, thus liberating H ions and making the solution more acid (less red). When free proteins are added to the epiphanin system, the system becomes less red (more acid). On the other hand, solutions containing an antigen plus its specific antibody do not produce a change in the epiphanin system, as the antigen and its specific antibody fix each other. This reaction is very clean-cut and definite; the strength of any solution containing free protein accurately can be titrated and the presence or absence of specific antibodies determined.

By studying the cooked antigens prepared as above, by means of this system, we found that they did contain free, soluble protein, but never were we able to demonstrate the presence of specific antibodies in the serum of sensitive rabbits. That the rabbits were sensitive was proved in that they all showed the phenomenon of Arthus after daily intraperitoneal injections of 2 c.c.; when larger doses were given (5 c.c.) the animals showed all of the signs of protracted anaphylaxis.

Serum from these rabbits also was tested by a technique similar to the Kahn and the Meinicke tests for syphilis, with negative results. Antibodies could not be demonstrated by means of the complement-fixation test. Neither could precipitins be demonstrated with any regularity. Therefore, we concluded that injected, *cooked* allergens (the form in which they must sensitize people if they do so at all) do not provoke the formation of specific antibodies, and that allergy to foods is not caused by the union of antigen and its specific antibody.

However, it was noted that when rabbits were injected with any of the cooked antigens, some

substance appeared in the serum which caused a greatly increased shift in the epiphanin system. For example, if the serum taken from a rabbit before it had been injected (non-sensitive) was titrated by means of the epiphanin system, the serum usually would show an endpoint in a dilution of approximately 1-80. Two weeks later, after having received daily intraperitoneal injections (2 c.c.) of any antigen, serum from the same rabbit would show an endpoint in a dilution of 1-2500. Plainly something was changing in that blood.

Another interesting phenomenon also was noted in this connection. If a sensitive rabbit was titrated on the same day on which the serum was taken, we would, for example, find a titration endpoint of 1-2500. If this same serum were permitted to stand in the icebox overnight, the activity of the serum in the epiphanin system would drop to 1-320. Then, if the same serum were titrated 24 hours later, it would be back to normal, *viz.*, 1-80. In short, the agent which was causing the shift in the epiphanin system was extremely labile; heating to 50 degrees C. for 30 minutes caused the substance to disappear entirely.

On the supposition that this unknown substance or agent might be an enzyme (one of Abderhalden's "protective" enzymes) we tested the sera of sensitive rabbits with 5 per cent suspension of starch and iodine, and with a ½ per cent solution of albumin. One cubic centimeter of the starch suspension was added to each of six tubes. The first tube received .05 c.c. of pure serum; the second, 0.1 c.c.; the third, 0.2 c.c., and so on. Similar tubes were set up containing varying quantities of protein (albumin) and olive oil. In this manner we demonstrated in the serum a substance or agent which in a dose of .05 c.c. of pure serum was able completely to digest the standard testing solutions in 24 hours. Normal rabbit serum also was found to contain this agent, causing complete digestion in a dose of 0.1 c.c. of a 1-10 dilution. Normal human serum was found to contain this agent, causing complete digestion in a dose of 0.2 c.c. of pure serum. Rabbit serum, therefore, would appear to contain more of this pancreatic-enzyme-like substance than does human serum.

The serum of sensitized rabbits next was tested against the cooked antigens and it was found that digestion took place in the same dosage as was found effective against the starch and albumin mixtures. The reaction was found to be non-specific, the serum digesting any protein equally well. We concluded from the above experiments that normal rabbit serum contains an amylase-like agent which hydrolyzes starch to sugar, a trypsin-like agent which racemizes all proteins, and a fat-splitting agent. These "enzymes" are found in the sera of all normal animals in a remarkably constant concentration.

BLOOD SERUM TEST FOR ENZYME ACTION

Subsequently, we made a study of a large number of human sera. It was found that normal human sera always contain these enzymes in a concentration which is so constant that their determination can be used as a specific test. If 0.2 c.c. of pure human serum is added to a tube containing 1 c.c. of 5 per cent starch-iodine suspension, complete digestion will take place in 24 hours, when incubated at body temperature.

During the course of these experiments it was further learned that enzymes do not always act as catalyzers, merely accelerating a reaction as oil facilitates the running of a machine, the enzyme itself not appearing in the end-product; but that they are "bound" or fixed chemically by the substance upon which they act. A given quantity will digest completely the testing solution; a lesser quantity will not cause complete digestion no matter how long it is incubated.

Because three enzymes would appear always to be found in normal sera, and because they acted exactly like the pancreatic enzymes, splitting proteins, carbohydrates and fats, and because they did not exhibit a specific action, digesting all food substances equally well, we concluded that the serum enzymes were in fact pancreatic-like enzymes which had been absorbed—free—into the blood stream. And because these enzymes are found in all normal human sera in a concentration in which 0.2 c.c. of pure serum will digest completely 1 c.c. of the standard starch mixture in 24 hours, we concluded that an agent acting like free pancreatic juice in the above concentration is a normal constituent of human serum. In fact, it may be pancreatic juice.

Our observations are in accordance with those of Boldyreff and his workers at Battle Creek (7). Long ago they demonstrated that the pancreas periodically secretes pancreatic juice, rich in enzymes, into the duodenum from whence it is absorbed into the blood where it can be demonstrated. The Abderhalden reaction depends upon these free pancreatic enzymes and not upon specific, protective enzymes as Abderhalden believed; this is the reason why the test has been found to be non-specific as a test for pregnancy.

Our findings (arrived at independently) differ from those of Boldyreff in one important respect. Boldyreff claims that the pancreatic enzymes are secreted periodically throughout the day, and that there are times during the day when the enzymes completely disappear from the blood. This has not been our experience. We have never encountered an instance in which the normal concentration could not be demonstrated.

SIGNIFICANCE OF BLOOD SERUM TESTS FOR "ENZYMES IN RELATION TO NUTRITION"

If a normal individual, one who has no difficulty with any type of food in any quantity, whose weight is normal and whose blood contains the normal complement of free enzymes, is given a diet in which the quantity of protein, carbohydrate and fat is greatly increased, the blood will still show the same concentration of free enzymes.

However, if one observes an underweight individual, one who is habitually underweight and in whom no amount of food will cause a weight increase, there is a different situation. On his normal diet (which, however, is insufficient to maintain normal weight) such an individual will show the normal quantitative values for free serum enzymes. But if his diet is increased, the enzymes will disappear from his blood. Inasmuch as the blood is taken from the patient at the same hour each day, this disappearance of the enzymes cannot be due to the periodic disappearance of "enzymes" as claimed by Boldyreff.

In short, normally as a result of the stimulation of food intake, the pancreas may be considered to secrete a sufficient quantity of enzymes to unite with all of the food taken, plus an excess—which it seems may be absorbed free into the blood stream. This is in accordance with the findings of Boldyreff. But the underweight individual appears to be unable to secrete sufficient enzymes to digest even a ration which will maintain his normal weight. If he is given an increased ration, he is unable to digest all of the food, perhaps because an insufficient quantity of enzymes is present; because the food fixes all of the enzymes, no free enzymes pass into the blood stream and the normal serum enzymes disappear from the blood. From the concentration of enzymes in the serum of an individual on his regular ration and after taking a test meal consisting of a greatly increased ration, it appears that the serum taken at the same hour each day, may be regarded as a direct measure of that individual's pancreatic function.

All the chief pancreatic ferments—those splitting carbohydrates, proteins and fats—are being secreted by the secretory cells of the pancreas at the same time and are inseparable in the pancreatic juice. Some physiologists believe that they form one common chemical molecule. This may explain why protein, carbohydrate and fat metabolism is affected if any of the enzymes are affected (8). This is in accordance with our findings; the concentration of all of the pancreatic enzymes always was found in the same relative proportions. If any of them were present, they were all present in the same relative concentration. When the concentration of amylase decreased, they all decreased. We have used this observation to simplify the technique of our test. Instead of testing for the presence of all three of the pancreatic enzymes, we have simplified the procedure by testing for amylase alone. Practically, the test is performed as follows:

APPLICATION OF THE SERUM TEST FOR ENZYMES

The first day the patient reports at a given hour and his blood is taken. In about two hours, or just so soon as the serum separates from the clot, it is centrifuged free from cells and three tubes are set up. Tube one is the control; it receives 1 c.c of the standard starch-iodine suspension; tube two receives 1 c.c. of the starch-iodine suspension plus .05 c.c. of pure serum; tube three receives 1 c.c. of the starch-iodine suspension plus 0.1 c.c. pure serum. The tubes are incubated at body temperature for 24 hours. Tube one, of course, never shows any change. Tube two, in a normal individual, usually shows almost, but not quite, complete digestion. Tube three usually shows complete digestion.

The patient is then instructed to double his regular ration. If he has been in the habit of eating one egg for breakfast, he takes two; if he has been eating two pieces of toast, he is instructed to eat four pieces, and so on. We make no effort to place him on a definitely increased diet, containing a definite increase in the caloric value, but simply to have him definitely increase the normal food intake. He reports at the same hour the next day at which time again his serum is taken. This time, however, we set up eight tubes. Tube one is again the control; successive tubes contain .05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 c.c. of pure serum. The tubes again are incubated and are read in 24 hours. If the individual's serum will digest all of the testing solution *completely* in a dose of 0.1 c.c. the first day and will repeat the response on the second day, we assume that his "pancreatic threshold", or response is normal. On the other hand, if complete digestion takes place with 0.1 c.c. the first day, while it requires 0.6 c.c. for complete digestion the second day, the difference between 0.1 and 0.6, *viz.*, 0.5, we regard as a direct measure of pancreatic inability or hypofunction.

SIGNIFICANCE OF BLOOD SERUM ENZYME DEFICIENCY IN ALLERGIC SUBJECTS

If underweight individuals who are unable to maintain the normal concentration of blood enzymes on the test ration are continued on the increased ration for several days, invariably they show evidences of food sensitization. They report herpes, pimples, canker sores and various indefinite digestive disturbances. If now they are given pancreatic enzymes (dry and enteric coated so as to be liberated in the duodenum) or the total food intake be reduced, the evidence of sensitization disappears. No longer do they complain of indigestion. They begin to increase in weight and the free enzymes again appear in the serum in normal concentration. This observation has led to a *present* conception of food sensitization which we summarize as follows:

In a normal individual (in whom a normal quantity of enzymes can be demonstrated in the blood serum) the pancreas secretes enzymes as a result of the stimulation of food sufficient to combine with *all* of the food taken, plus an *excess* which passes "free" into the blood. The normal serum-enzymes are an excess over and above the digestive requirements. They pass into the blood where it would seem they serve a protective function, acting as a "buffer solution", combining with any free food which has passed into the circula-

tion. Boldyreff is of the opinion that finally they are also absorbed by the body cells where they continue the digestive processes and thus maintain normal metabolism.

If such an individual overeats (takes our overfeeding test meal) the pancreas would seem to be stimulated to a greater degree and responds with a greater quantity of pancreatic juice, thereby producing sufficient enzymes for all of the food needs and adequate to maintain the normal "buffer" solution in the blood. In our experience, such an individual can maintain his normal weight, handle almost any quantity of food and never will become allergic.

On the other hand, the individual who has inherited (?) a poorly functioning pancreas, or whose glandular functions temporarily are depressed by reason of disease, gets into trouble when he surpasses the normal secretory threshold of his pancreas. If such an individual takes more food than can be digested, free protein passes into the blood. And because no excess enzymes have been secreted or are available, the buffer enzymes are absent and the protein continues to circulate as free protein which cannot be further split. Meanwhile in such abnormal situation it exerts its own physiological action which is essentially that of chemical irritation. Pure pancreatic juice is exceedingly irritating (8). It may be that the tissues are in this process sensitized, by reason of the free protein. From such anomaly, we believe that "sensitization" to foodstuffs results.

There has been some question as to whether whole, unracemized proteins ever enter the blood stream. When protein reaches the stomach, it meets HCl and pepsin which change part of it to acid metaprotein. Acid metaprotein is soluble and immediately may be absorbed into the blood stream. The food then passes into the duodenum where it encounters alkaline secretions which change any unchanged protein to alkali-metaprotein. Alkali-metaprotein likewise is soluble. Acid and alkali-metaproteins are normal constituents of blood serum, following meals. (One of us, P. A. O.)

Therefore, proteins are not always changed to amino-acids in the bowel; indeed, the greater part of digestion may be carried to completion in the blood stream. The blood, therefore, may be regarded as a more important final "digestive organ" than is the gastro-intestinal tract. Of course, the process is a continuous one; while a portion of the ingested protein is being absorbed into the blood as acid or alkali metaprotein, combined with pancreatic enzymes, the enzymes are acting upon another portion, changing it to proteoses, peptones and finally to amino-acids. The point we wish to make clear is that the gastro-intestinal tract essentially is a receiving and mixing organ where the food is mixed with acid or alkali and enzymes; because the metaproteins are soluble, it is our theory that the greater part of digestion takes place in the blood stream, and according to Boldyreff, finally in the body cells themselves.

In some respects, this observation is in accordance with the investigations of Walzer and his associates (10). Walzer obtained serum from a case very strongly allergic to fish and injected it into the skin of a non-allergic recipient, thereby rendering a portion of the skin passively sensitive to fish. The recipient then ate the fish in question and in a short time urticarial wheels appeared at the site of transfer. This experiment was repeated and the result again produced in a subject sensitive to eggs. Such observations prove that egg and fish protein normally are absorbed into the systematic circulation and carried through the blood to the site of transfer, still sufficiently unchanged as to be identified by a specific biologic reaction.

Most proteins consist of two parts: a protein nucleus which is common to all proteins, plus the addition of some other molecule. Such construction explains why all proteins are digested by the same enzyme, accounts for the biologic reactions manifested in skin tests, and it is the presence of the prosthetic group (not the protein nucleus) which results in the irritation of the body cells ("shock organs") a response which we know as sensitization. If the prosthetic group in the protein molecule is the cause of the specific biologic reaction and not the protein molecule, then one would expect to get positive skin tests in the case of compound proteins, while simple proteins would give a negative reaction. We are now working on this phase of the problem and later hope to have something to report.

Because metaproteins are soluble, part of the ingested protein passes into the blood stream before it has combined with the pancreatic enzymes, and we believe that it is the function of the buffer enzymes in the blood to "fix" and digest these free proteins. If buffer enzymes are not present, by reason of a hypo-functioning pancreas, the uncombined proteins continue to circulate as free proteins, apparently irritating all of the cells of the body. Then one observes what is called sensitization or allergy. Why these blood proteins irritate some tissues (shock organs) more than others still is unknown.

Because pancreatic enzymes do not exert a specific action, but will digest all proteins equally well, allergy results, not from an *excess of any one* specific protein, but from a *general excessive food* intake. Thus, treatment consists of a general reduction of the total caloric intake. If a total reduction within the limit of the pancreatic threshold still will permit normal weight, then no other treatment is necessary; but if the pancreatic threshold will not permit normal weight, then it becomes necessary to give as it were our horse help by introducing another horse into the team. Such help may follow the giving of dry pancreatic enzyme in sufficient quantity to maintain nor-

mal weight and to maintain the normal complement of serum enzymes.

It has been common clinical practice to test for the pancreatic enzymes in the duodenal secretions. Most men no longer perform these tests as rarely are the enzymes found to be absent. But according to the above work (and that of Boldyreff) to test for pancreatic enzymes in the duodenal secretions is not a rational procedure. The question is not whether an individual has *any* enzymes present, but how *much!* Does he have enough? The test must be quantitative, not qualitative. Merely to make a qualitative test for enzymes in the duodenal secretions is equivalent to testing the blood for hemoglobin to determine anemia. We know that hemoglobin always is present in blood; what we wish to know is *how much* is present. The only manner in which one can determine the quantity of pancreatic enzymes which is being secreted is by determining the blood serum enzymes. If sufficient pancreatic enzyme has been secreted to combine with all the food taken and to provide the buffer solution in the blood, then we know that that patient's pancreas is functioning normally. If that same patient is given the overfeeding test diet, a greatly increased ration, and the buffer enzymes still appear in the blood in normal concentration, then we know that the pancreas is equal to all demands. He is not sensitive to any food and he can maintain a normal weight. We think that a determination of the circulating enzymes, therefore, is the logical test for pancreatic efficiency, digestion and allergy.

Assuming this theory to be correct, then one should be able to explain every phase of allergy. A common example of allergy to foods is urticaria. Ordinarily a dose of salts, which relieves the bowels of excess food, and a reduced diet for a day, is all the treatment required.

From our viewpoint, the mechanism of acute urticaria is as follows: Our patient eats an excess of food. The undigested portion of starch and fat, being insoluble, remains in the gastrointestinal tract where it is the cause of gas and fermentative processes. In the stomach, part of the protein is changed to metaprotein and is absorbed. In the duodenum the remainder is changed to alkali-metaprotein, combines with the pancreatic enzymes present, and then gradually is absorbed into the blood stream; then the protein gradually is split through the various stages of derived proteins to amino-acids.

But because there occurred an insufficient quantity of pancreatic enzymes (when the patient's food intake surpassed his pancreatic threshold) part of the metaprotein passes free, uncombined with enzymes, into the blood. For the same reason (pancreatic hypofunction) the buffer enzymes are absent from the blood and the free uncombined metaproteins remain unchanged in the circulation. Meanwhile the patient has purged himself, placed himself on a limited diet which permits the pancreas to catch up, as it were, the buffer enzymes are restored, the free metaproteins in the blood are digested and there occurs spontaneous recovery.

On the other hand, a patient who habitually surpasses his pancreatic threshold, especially in the realm of his usual diet (staple foods) never "catches up". Because the circulating metaproteins are not digested, they continue to irritate the tissues, perhaps forming loose compounds with the body cells, which, because such compounds are unphysiological, are poisonous. This is a supposition, a working of hypothesis and has not been proved; it requires further study. However, Walzer's observations would seem to indicate that some such mechanism is at work in the phenomenon which we call sensitization.

Treatment of this type of patient consists of a reduction in the total food intake. If the subject can maintain his normal weight on the reduced ration, no other treatment is necessary. If he is unable to maintain his normal weight, in addition to the buffer enzymes in the serum on the reduced ration, assistance may be secured from dry pancreatic enzymes administered to augment the normal but, in such patient, deficient pancreatic function.

Allergy or sensitization to foodstuffs, explained on the above bases, therefore, is not a pathological condition but a pathological exaggeration of a normal physiological mechanism. The above data explain why 60 per cent of the population have allergic manifestations at some time in their lives, and why most of such instances may be acute but, usually, clear up spontaneously. This conception would seem to indicate that inheritance has nothing to do with the allergic state except inasmuch as one may or may not inherit a functionally adequate pancreas. All that is necessary for the appearance of the allergic state is that one be exposed to massive doses of food, a quantity of food sufficient to surpass the individual pancreatic threshold at a particular time or constantly.

The above data would seem to explain why allergy to foods practically is unknown in the Orient. Because of the low scale of living, probably the Oriental rarely gets sufficient food to exceed his needs, *viz.*, surpass his pancreatic threshold. They also explain why acute allergy commonly clears up without treatment, and why many people lose their sensitizations after prolonged avoidance of proteins (although it would appear that it is the *total* reduction of food which acts beneficially and not the elimination of *any specific* protein), and why many patients can maintain a state of "allergic balance" by continual dietary restriction.

Our data and our theory seem to explain why allergic individuals usually are sensitive to foods with which they come into continuous contact. It follows that, if one only eats oysters occasionally, it would be difficult for this protein to cause trouble. Sensitization is more likely to follow the ingestion of such staples as beans, bread, eggs, meats, milk. If one exceeds the pancreatic thresh-

old, naturally he will do so in the realm of these staples; because they *are* staples in the average dietary they are more likely to produce chronic sensitization. Our theory also explains the uniform lack of success following desensitization in food-sensitive individuals. Desensitization fails because allergy is not caused by any *one* foodstuff, but on the basis of total food intake being too large for the individual.

Sensitization to foods is the most frequently noted manifestation of clinical hypersensitiveness (allergy). It does not always manifest itself as a definite disease syndrome, such as asthma, but commonly causes minor symptoms, as headache, "indigestion" (which cannot be accounted for on an organic basis), canker sores (which refuse to depart until the underlying pancreatic secretory deficiency is corrected), "pimples" (not acne), herpetic eruptions and the like.

SUMMARY

1. Most of the protein ingested is not split to the stage of amino-acids in the gastro-intestinal tract. A large part of the protein is absorbed into the blood as acid or alkali metaprotein and other derived proteins. The gastro-intestinal tract essentially is a receiving and mixing mechanism. Digestion is started in the gastro-intestinal tract but is continued and completed in the blood stream.

2. Normally, sufficient pancreatic juice is secreted to combine with all of the food eaten and to provide an excess which passes free (uncombined) into the blood stream, where it acts as a buffer solution, combining with and digesting any food which has been absorbed unmixed with enzymes.

3. Blood serum normally contains free pancreatic enzymes in a definite and constant concentration. These enzymes can be demonstrated by a simple test which we have described.

4. The concentration of pancreatic enzymes in the blood serum of an individual on a regular ration, compared with that after taking a "test meal" consisting of quantitatively a greatly increased total ration, appears to be a direct measure of that individual's pancreatic (digestive) function.

5. It is probable that "hypersensitiveness" to foods is caused by an excess of free food (free of enzymes) in the blood serum, and that this excess is caused by a low pancreatic threshold (hypofunction).

6. In our opinion, the state of "allergy" to foodstuffs can be determined by ascertaining the concentration of free amylase in the serum before and after a test meal.

7. The rational treatment of sensitization to foods lies in the reduction of the total food intake. If the patient can maintain normal weight and adequate buffer enzymes on the reduced ration, no other treatment is necessary. If he is unable to do so, it would seem that dry pancreatic enzymes must be administered to make up the shortage.

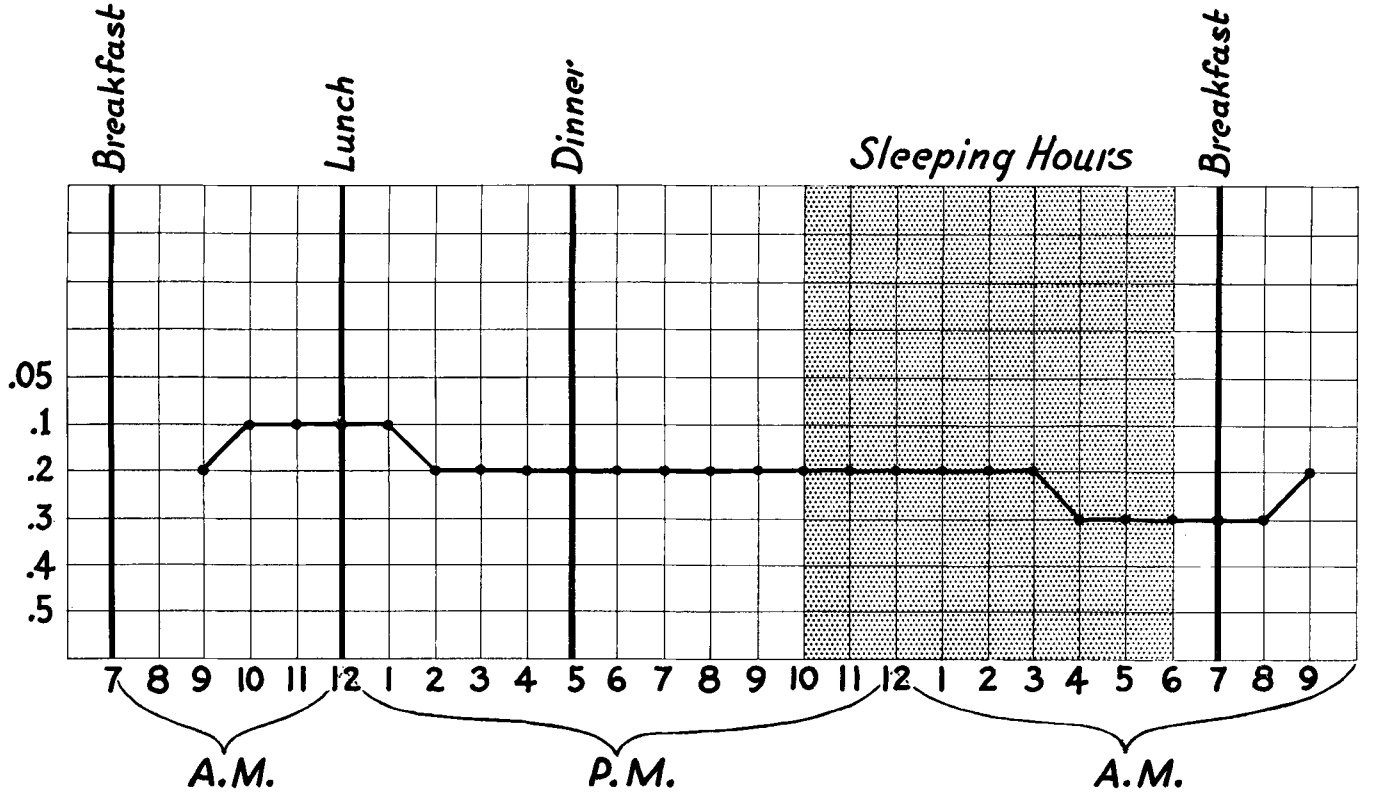

Chart showing concentration of pancreatic enzymes in normal human serum. Note that the enzyme concentration is practically constant throughout the 24-hour period. Food intake and sleep (empty stomach) have no influence on concentration of enzymes in normal human serum, the enzymes passing into the blood steadily and in a practically constant concentration. The slight rise after breakfast and the slight fall at 4 A. M. are of no significance. (.05, 0.1, 0.2, 0.3, 0.4, 0.5 c.c. were the quantities of pure serum used in the tests. The serum was tested against a standard 5 per cent starch-iodine suspension, which was incubated for 24 hours at body temperature.)

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ABSTRACTS

CHARLES M. BLUMENFELD.

Endocrinology. Weight Changes in the Suprarenal Glands of Albino Rats on Vitamin E Deficient and Fat Deficient Diets. 18:367-381, May-June, 1934.

Blumenfeld has demonstrated a relationship of the suprarenal to vitamin E and to fat metabolism. Rats deprived of vitamin E and killed during the second pregnancy had suprarenals, the cortex of which was questionably hypertrophied, but the medulla of which was definitely atrophied. Rats maintained on a vitamin E deficient diet and carried through a first pregnancy, then were fed vitamin E and killed during a second pregnancy, had significantly enlarged suprarenals due entirely to cortical hypertrophy. The medulla returned to a normal weight. A fat-free diet produced in male and female albino rats a relative atrophy of the suprarenals due to both cortical and medullary decrease. Curing the symptoms of this diet by feeding fatty acids, chiefly linoleic, did not cause a return of the suprarenal weight to normal. The nature of these relationships is as yet not elucidated.

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Experimental Gout in Turkeys. Proceedings of the Staff Meeting of the Mayo Clinic, Division of Experimental Medicine, September 19, 1934; pages 560-1.

Gout apparently is a disease of man, birds and reptiles. No definitely proved cases of gout have been observed in lower animals other than the two named. Both visceral and articular gout occur spontaneously in birds; the former is thought to be the more prevalent. Among domesticated fowl gout occurs more frequently in chickens than in waterfowl, and rarely is it seen in pigeons. Gout has been observed in birds of prey in zoological gardens.

During 1933 we had the opportunity to observe spontaneous tophaceous gout in five flocks of turkeys. Since turkeys apparently are susceptible to this disease, and are an easy bird to work with, we attempted to produce gout in them experimentally, for study. We used twenty turkeys in our experiments. They were placed two each, in ten pens. Five of these pens were small cages, measuring 26 by 26 inches (65.96 cm.), within a building, and the remaining five pens were outside runs affording ample exercise and a wide range of temperature. Five combinations of diet were fed to these turkeys. The turkeys in outside and inside pens were fed identically. This gave us the opportunity to study the effects of diet, the effects of restricted exercise, and a combination of the two. The turkeys were fed the following five diets: (1) commercially prepared turkey food containing 20 to 24 per cent protein, (2) commercially prepared turkey food and ground raw horse flesh in equal quantities, (3) commercially prepared turkey food with 5 per cent urea added; (4) commercially prepared turkey food and fresh green spinach, and (5) commercially prepared turkey food and cracker meal in equal quantities.

All turkeys were weighed at approximately the same hour once each week. At this time we also procured 1 c.c. of blood from the wing vein of each, for determinations of blood uric acid.

Little difference occurred which could be attributed to restriction of exercise, except that the restricted animals took less food. This was probably due to the fact that the cages were in a building which reduced the hours of daylight, so that these birds remained on the roost longer than their outdoor neighbors; consequently the value for uric acid in the blood of the restricted birds usually was found to be slightly, but not significantly, lower than that in the blood of the outdoor birds. The birds which were on the standard diet showed a range of blood uric acid, from time to time, of between 4 and 10 mg. per cent, and the birds which received the same diet, with green leaves added, showed a similar range. The diet with meat added gave high values for blood uric acid, from 5 to 22 mg., and the diet with urea added gave similar changes, from 5 to 20 mg. The addition of cracker meal somewhat reduced the level of uric acid in the blood, from 3 to 5 mg.

Part of the uric acid metabolism of birds is like that of mammals, in that uric acid is an end product of purine metabolism, which in turn is part of nuclear metabolism. The major portion of the uric acid formed and excreted by birds, however, is derived from protein or nitrogenous metabolism. These animals possess capabilities for a special process by which urea or ammonia is converted to uric acid by the liver and is excreted by the kidneys as uric acid. Little urea is found in the urine, and the concentration of urea in the blood is low. There are daily variations in the amount of uric acid in the blood, similar to the variations found in the blood urea of mammals. After feeding, the concentration of blood uric acid increases, depending on the amount of protein or nitrogenous substances in the diet, and as assimilation is completed, the value for blood uric acid slowly falls to a fasting level. The bird with free access to food usually eats at frequent intervals, so that the value for blood uric acid almost always is at digestion levels.

Definite gouty tophi appeared on the feet of only those birds in the blood of which the value for uric acid was 15 mg. per cent for at least two weeks. As far as we could determine, the elevated concentration of uric acid of the blood preceded the deposition of tophi and the appearance of symptoms. After symptoms were present, the value for uric acid in the blood usually fell, because less food was consumed. Some of the lesions progressed, to become extremely large and numerous, whereas others developed and remained stationary, but no regression in size or number of lesions was observed.

On the basis of these observations, we feel that tophaceous gout in turkeys depends on marked increase in concentration of uric acid in the blood. The value for blood uric acid may be increased by an increased concentration of nitrogen (either protein or urea) of the diet, or by renal insufficiency.

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