

SPECIAL ARTICLE

Glycemia and Immune Responses

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Feed a cold."*†

IN THIS article an attempt will be made to correlate the immune response of an animal with the degree of its glycemia (see below for precise definition). The medical literature contains several observations from which such a correlation can be inferred, or which explicitly demonstrate it. Some of these observations are old and forgotten, others are very recent. They span a period of over 40 years, and cover practically every major chapter of immunology.

But the correlation is not easy, because the experimental evidence on which it must be based is still fragmentary. In attempting this correlation now, certain generalizations that may appear to be far-fetched could not be avoided. The author believes, however, that the attempt is justified because the existence of a relationship between the degree of glycemia *in vivo* and immune responses will be brought to the attention of investigators. As a result, the gaps in the hitherto rather fragmentary evidence may be bridged more quickly.

For the purpose of this article, the term immune response will be used to denote both (1) the various types of protective immunity and (2) the various types of hypersensitivity.

Hypersensitivity will be divided into three types: (1) immediate hypersensitivity; (2) delayed hypersensitivity, and (3) "parahypersensitivity", which comprises the type of phenomena known generally as the "non-immunological equivalents of hypersensitivity reactions".¹²

The immune responses all have in common a reaction between a foreign chemical entity, referred to here as the antigen, and an intrinsic chemical entity, the antibody. The parahypersensitivities are considered to be an exception to this. The signs and symptoms they produce are similar to those of other hypersensitivities; they are provoked by well-defined foreign chemical entities, which might also be called antigens, but no antibody has yet

ABSTRACT

The intensity of experimental and clinical immune responses was correlated with the degree of glycemia of the reacting subject. Hyperglycemias resulting from overdosage with sugars, cortisol, adrenaline, or from diabetes inhibit the anaphylactoid reactions; anaphylaxis, and the tuberculin reaction; but potentiate infections. Hypoglycemias resulting from fasting, insulin and adrenalectomy potentiate the anaphylactoid reactions, anaphylaxis, and the tuberculin reaction; but inhibit infections. The hypothesis is proposed that hyperglycemia inhibits certain antigen-antibody combinations; this results in an inhibition of hypersensitivity, but an aggravation of infection.

been found that would correspond to the antigen.

In this article, an attempt will first be made to link some of the parahypersensitivity reactions more closely to the other immune responses. This is necessary because it is in the parahypersensitivities that the correlation between the degree of glycemia and immune responses has been studied most extensively to date. Then, a definition of the term glycemia, as used in this article, will be given. Evidence will be presented concerning the influence that the degree of glycemia exerts on immune responses in general. And finally, a working hypothesis will be formulated to explain partly this influence.

The Relation of Parahypersensitivity to Immune Responses

The anaphylactoid reaction, and the histamine and serotonin shock-like states may be considered to be examples of parahypersensitivity. They differ from other immune responses in general, and from anaphylaxis (an immediate hypersensitivity) in particular, in two main respects:

1. They occur without the concomitant appearance of an identifiable antibody; whereas, in anaphylaxis, an antibody appears and can be transferred passively by serum from one animal to another.

2. The anaphylactoid reaction and the histamine and serotonin "shocks" are provoked by the first injection of the antigen—they do not require a

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†The English version of an old medical adage. In olden times, what was known as "the fever" was usually caused by bacterial infection. According to the hypothesis proposed in the present article, hypoglycemias inhibit the signs and symptoms of infection. Hypoglycemia may be induced by starvation; hence, the old recommendation "starve a fever" was justified to some extent.

"The cold" involved a running nose, tearful eyes, sneezing and headaches; very often these signs were the result of hypersensitivity to pollens, etc. According to the present hypothesis, hyperglycemia inhibits the signs and symptoms of hypersensitivity. Hyperglycemia may be induced by eating carbohydrates. Hence, the old recommendation "feed a cold" was appropriate.

period of sensitization to the antigen; whereas, in anaphylaxis, the animal must undergo a period of sensitization to the antigen. During this period the antibodies are built up. Only subsequent re-injection of the antigen will cause a potent antigen-antibody reaction, which results in anaphylactic shock.

However, it was found recently that the dextran-induced anaphylactoid reaction can be transferred passively by serum from donor to acceptor rats. The transferable anaphylactoid-reaction-inducing factor is potentiated if the donors are presensitized over a period of a few days with the antigen, dextran.⁹

Furthermore, Ganley¹⁵ reported that in mice sensitized with *Bordetella pertussis* hyperglycemia inhibits not only the histamine or serotonin toxicity but also the anaphylaxis. In contrast to this, hypoglycemia exerts a sensitizing effect.

On the basis of these observations, the list of similarities between the two parahypersensitivities, that is, the anaphylactoid reaction and the histamine or serotonin shocks, and true hypersensitivity (anaphylaxis) is becoming longer: (1) The signs and symptoms in all of them are similar. This includes the release of histamine and the preventive action of antihistaminics. (2) The anaphylactoid reaction, like anaphylaxis, can be transferred passively in serum. Therefore, some sort of transferable antibody exists in both.

3. The transferable antibody can be built over a period of time under the sensitizing effect of an antigen.

4. The most important similarity appears to be the fact that the anaphylactoid reaction and histamine or serotonin "shocks" are influenced by changes in glycemia in a manner similar to that of certain true hypersensitivities.

The Degree of Glycemia

The sugars of an animal are present in its body fluids (extracellular sugar) and inside its cells (intracellular sugar). There is a constant interchange between certain sugars of the fluids and those of the cells. Some sugars may leave the fluids and enter certain cells, or vice versa. The amount of sugar in the body fluids at any one time is called the glycemia. As this amount varies, so does the glycemia, and therefore one may speak of the degree of glycemia at any one time.

Those body fluids that contain the sugars are also known by the name of extracellular sugar space. The volume of this space varies somewhat with different sugars. In general it comprises the blood, the extracellular fluids, and also those parts of cell walls that are bathed with the fluids. Thus, the sugar space is composed of different, although interconnected, compartments.

Glycemia is measured most readily in the blood compartment. It is assumed that the degree of blood glycemia is a reflection of the degree of glycemia

in all the body fluids. This assumption has important limitations. For example, blood glycemia may not necessarily reflect the rapid local changes of glycemia in the interstitial fluids that bathe the cell walls.

For the purpose of this article the term "degree of glycemia" shall mean the total amount of sugars in the body fluids at the time when an immune response takes place.

Since glucose is the main physiologic sugar, the degree of glycemia depends mainly on glucose. However, glycemia may be increased also by the parenteral administration of other monosaccharides (galactose, fructose) and disaccharides (lactose, sucrose).⁸

Most immune reactions either take place entirely in the body fluids or at least occur partly there. Thus, the reaction between free antigens and free antibodies occurs in the body fluids. The reactions between free antigens and antibodies, which may be bound to the exterior of cells, also take place in the body fluids. The same would be true of a reversed situation where free antibodies would react with antigens bound to the exterior of cells. Finally, there is the case of free antigens that react with intracellular antibodies. Some steps of this reaction involve the alteration of the cell wall from the exterior under the influence of the antigen. Thus some stages of this immune reaction also take place in the body fluids. The same would be true of a reversed situation where free antibodies would react with intracellular antigens.

The following observations indicate that the immune response is influenced by the total amount of sugars in the body fluids, rather than by the amount of intracellular sugar. Procedures that increase the amount of sugar in the body fluids inhibit several hypersensitivity reactions, as is illustrated in more detail later on. These procedures include the parenteral administration of large doses of sucrose which is known not to enter the intracellular space. On the other hand procedures, such as the administration of insulin, that remove sugars (mainly glucose) from body fluids potentiate several hypersensitivity reactions. One effect of insulin is to intensify intracellular glucose metabolism. A similar intensification is obtained by overdosing the animal with glucose; however, overdosage with glucose inhibits the hypersensitivity reactions. Therefore the potentiating effect of insulin does not appear to be due to the intensification of the intracellular glucose metabolism but rather to the lowering of extracellular glucose in the body fluids.

It is convenient to distinguish three degrees of glycemia: (1) euglycemia, (2) hypoglycemia, and (3) hyperglycemia.

Numerous experimental procedures are available to allow alteration of sugar homeostasis or metabolism in such a way as to achieve either a hypoglycemia or a hyperglycemia. Furthermore, the resultant change in glycemia may be either primary or secondary.

The following are a few procedures that result in a hypoglycemia: (1) fasting and starvation; (2) administration of insulin or of insulin substitutes; (3) adrenalectomy; (4) hypophysectomy, and (5) thyroidectomy or the administration of thyroid hormone(?).

Procedures 1 and 2 primarily affect sugar metabolism; the result is a primary hypoglycemia accompanied as a rule by low blood sugar levels. Procedures 3 to 5 affect the sugar metabolism only secondarily. They result in a secondary hypoglycemia that may subsequently become obscured or even neutralized by various compensatory mechanisms.

The following are a few procedures that result in a hyperglycemia: (1) The administration by any route of large doses of glucose, and the parenteral administration of other sugars; (2) diabetes, including alloxan diabetes; (3) administration of glucocorticoids, especially cortisol; (4) administration of adrenaline; (5) administration of growth hormone; (6) administration of glucagon, and (7) thyroidectomy or the administration of thyroid hormone(?).

Procedures 1 and 2 again primarily affect sugar metabolism. They result in a primary hyperglycemia accompanied as a rule by high blood sugar and urinary sugar levels. Procedures 3 and 4 may also be considered to result in a primary hyperglycemia. Procedures 5 to 7 affect the sugar metabolism only secondarily. They must be applied for long periods of time, and they result in a secondary hyperglycemia that may subsequently become obscured or neutralized by various compensatory mechanisms.

Degrees of Glycemia and Parahypersensitivity

As a rule, hypoglycemia induced in a variety of ways markedly potentiates the parahypersensitivities that have been studied to date.

The administration of insulin to rats potentiates the anaphylactoid reactions induced by dextrans,^{1-3, 16, 22} egg-white polysaccharide,^{3, 22} and soluble glycogen.³ Insulin substitutes,⁵ fasting,⁶ adrenalectomy,^{14, 23} and the administration of thyroid hormones, as confirmed recently by West and collaborators,²³ also potentiate the anaphylactoid reaction induced in rats by dextran or egg-white polysaccharide.

Apparently, hypoglycemia only potentiates the anaphylactoid reactions induced by a polysaccharide antigen, such as those mentioned above. If the antigen is Compound 48/80, a non-carbohydrate, the anaphylactoid reaction is not potentiated by hypoglycemia.¹⁶

The administration of insulin to alloxan-diabetic mice sensitized with *B. pertussis* reverses the protective effect exerted by diabetes against the toxicity of histamine or serotonin;¹⁵ this toxicity is also increased in animals treated with thyroid hormone.²³ Although histamine and serotonin are not carbohydrates, the possibility that they react in the

body with some carbohydrate moiety cannot be excluded.

On the other hand, the anaphylactoid reaction and histamine or serotonin toxicity are markedly inhibited or totally abolished by hyperglycemia induced in a variety of ways. Alloxan diabetes inhibits¹⁶ or totally abolishes⁴ the anaphylactoid reaction induced by dextran or by egg-white polysaccharides in rats. The two types of anaphylactoid reaction are inhibited by thyroidectomy²³ and are totally abolished, in rats, by overdosage with glucose,⁷ galactose, fructose, and with the disaccharides, lactose and sucrose.⁸ Similar overdosage with substances other than sugars exerts no such effects. Cortisol inhibits the dextran anaphylactoid reaction and this inhibition is removed by insulin.¹ Alloxan diabetes considerably diminishes the toxicity of histamine or of serotonin in mice sensitized by *B. pertussis*.¹⁵

Of special interest is the finding of Goth that the administration of small amounts of 2-deoxyglucose, which is a glucose antimetabolite, very effectively inhibits the anaphylactoid reaction induced in rats by dextran or egg-white polysaccharide. 2-Deoxyglucose is known to substitute itself for glucose in various enzymatic reactions and to block them.¹⁷

Degrees of Glycemia and Delayed Hypersensitivity

It has been known for some time that the tuberculin reaction, which is a delayed type of hypersensitivity, is influenced by the degree of glycemia of the reacting animal. This was recently re-confirmed by Thompson.²⁴ It may be noted that polysaccharide antigens are involved in this reaction. In general, hypoglycemias induced in various ways increase the sensitivity of guinea-pigs to the tuberculin reaction, and hyperglycemias decrease the sensitivity. The reader is referred to an article by Long.²⁰

It may be relevant at this point to recall that the blood group substances consist in part of oligosaccharides, and that the *in vitro* immunologic reactions of these substances are influenced by monosaccharides.¹⁸

Little is known about the effect of glycemia on the immune responses that accompany tissue and organ transplantation. However, it is common practical experience that the pretreatment of animals with cortisol inhibits the immune reactions that accompany such transplantations; the result is a greater number of "takes". This is particularly true of tumour transplantation.²⁵ In this case, the inhibiting effect of the cortisol-induced hyperglycemia on the immune response also has to be taken into consideration.

Degrees of Glycemia and Immediate Hypersensitivity

As early as 1920 to 1925 it was noted that during fatal bacterial anaphylaxis in rabbits there is a rise

of blood sugars "which attain an extremely high value at the time of death".²⁷ Liver glycogen may disappear in such animals. This observation could be interpreted now as an attempt on the part of the animal to protect itself against anaphylaxis through hyperglycemia, an interpretation that would not be inconsistent with recent findings.

Rats are notoriously resistant to the anaphylaxis caused by horse serum or egg white, and to other types, when the antigen is administered without adjuvants. The resulting anaphylactic shock is then only occasionally fatal in this species. But hypoglycemia, induced at the time of the anaphylactic shock, by the injection of insulin or by fasting, increases the mortality of rats to 40-60%.¹⁰ Histologic examination of the ileum and of the thymus reveals an aggravation of the anaphylactic lesion in both.¹⁰ Insulin also increases the anaphylactic mortality rate in rats sensitized with horse serum plus the *Bordetella pertussis* adjuvant,²⁴ and reverses the protective effect of alloxan diabetes.

Hyperglycemias, on the other hand, exert a protective effect. The administration of massive doses of glucose to hypoglycemic rats almost completely restored the resistance to the anaphylactic shock produced by horse serum or egg white. This was true even when the rats received a simultaneous administration of insulin or were fasted for 48 hours; the mortality in these circumstances should have been around 40-60%.¹⁰ Histologic examination revealed a diminution of anaphylactic lesions in both the ileum and the thymus.¹⁰ Alloxan diabetes protects 50% of rats against anaphylaxis produced by horse serum plus the *B. pertussis* adjuvant,²⁴ or produced by *B. pertussis* alone.¹⁵ As mentioned above,²⁴ this protection can be reversed by the administration of insulin.

It is well known in clinical practice that the administration of hyperglycemic doses of adrenaline is beneficial in relieving certain types of bronchial asthma of allergic origin. Although it was generally accepted that the beneficial effect of adrenaline is due in this case to bronchodilation, its hyperglycemic action has also been implicated.¹³ The fact that the administration of large doses of glucose also exerts a beneficial effect in such patients¹⁹ lends further support to the hypothesis that the degree of glycemia also plays a role in this condition.

In our experience, rapid oral administration of large doses (100 to 150 g.) of glucose to children relieves them of coughing of allergic origin.¹¹

Mechanism of the Influence of Glycemias on Immune Responses

In the introduction it was stated that the purpose of this article was to draw attention to the growing number of inter-relationships between the degree of glycemia and the immune responses. The inter-relationships are still too fragmentary to allow the formulation of a hypothesis that would explain

them. On the other hand, they should not be ignored. Therefore, the best that can be done at present is to advance a working hypothesis, which will be subject to further experimentation.

The working hypothesis at this early stage is very simple. It assumes: (1) that a multiplex reaction takes place between an antigen and an antibody in most immune responses; (2) that hyperglycemia inhibits and hypoglycemia potentiates the antigen-antibody reaction if the reaction involves a carbohydrate moiety, and if it occurs at least partly in the body fluids.

The antigen-antibody reaction appears to be responsible for the signs and symptoms of hypersensitivity. If hyperglycemia inhibits this reaction, it would not be surprising for it to inhibit also the signs and symptoms of hypersensitivity. In hypoglycemia, the reverse would be true.

Carrying this speculation one step further leads to intriguing possibilities with respect to protective immunity.

Degrees of Glycemia and Protective Immunity

The influence of glycemia on protective immunity is poorly understood at present. This stems from the fact that the systematic experimental studies of the relationship between the degrees of glycemia and immune responses have been started from the wrong end, so to speak (Fig. 1). These studies started with the parahypersensitivities instead of with protective immunity itself. Such evidence as exists comes mainly from clinical observations. The problem is now being studied in our laboratory.

If the antigen-antibody reaction *in vivo* is inhibited by an excess of glucose, then infection of the organism by bacteria (and viruses) should be facilitated during hyperglycemia, when the bacterial antigen is less likely to be neutralized by the antibody. During hypoglycemia, the initiation of infection should be more difficult. Therefore, the signs and symptoms of infection should be aggravated by hyperglycemia and inhibited by hypoglycemia. This appears to be the exact opposite of reactions seen in the hypersensitivities.

It is a well-established fact that a predisposition to infection is a common attribute of clinical diabetes, and that this complication disappears when diabetes is controlled.²⁸ Medical literature prior to 1940 contains numerous articles on this subject, such as that of Moen and Reimann.²¹

On the other hand, clinical and experimental septicemia resulting from chronic overdosage with cortisol has generally been attributed to a "lowering of body resistance" and to the "antiphlogistic" action of this glucocorticoid. Cortisol indeed inhibits antibody formation in certain instances of protective immunity, but when administered in large doses it regularly induces a hyperglycemia. The aggravating effect of this hyperglycemia on infection should not be ignored.

In the guinea-pig, the local injection of hyperglycemic doses of adrenaline together with certain bacteria triggers a septicemia, gas gangrene and death. Used as a control, a local injection of the same dose of bacteria without adrenaline has no such effects.³⁰ Gas gangrene was also triggered by an injection of hyperglycemic doses of adrenaline to patients suffering from allergy.³¹ In all of these cases, the enhancement of infection was attributed to the vasoconstricting action of adrenaline. As a

feed-back mechanisms that release insulin or adrenaline. But, although glucose appears to regulate the severity of the immune response to a certain degree, it is only one of many factors operating in this regulation.

The degree of glycemia itself is closely regulated by hormonal mechanisms. Therefore, sugars, especially glucose, appear to provide an identifiable link between immunological and hormonal defenses, and even between the nervous defenses,

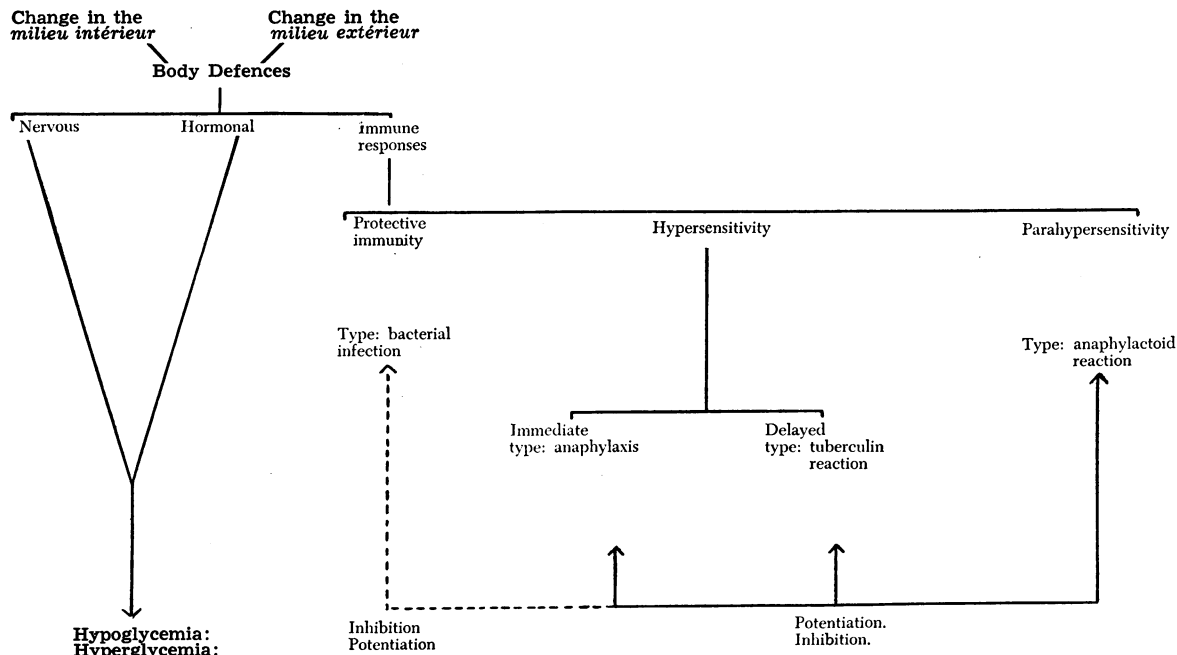


Fig. 1.—The influence of hypoglycemia and hyperglycemia on immune responses, and the correlation of the degree of glycemia with nervous and hormonal body defenses.

result the oxygenation of bacteria-containing tissues would be lowered and the proliferation of anaerobic bacteria enhanced. Such an interpretation is plausible. However, it does not exclude the possibility that the adrenaline-induced hyperglycemia inhibits the local preventive immune reaction, thus enhancing bacterial proliferation. This particular problem merits careful reinvestigation.

The Degrees of Glycemia and Body Defences

The evidence available to date indicates that the degrees of glycemia present in an animal influences the quantity of its immune response. Further experimentation will confirm or discredit this conclusion. Exceptions to it already exist. Some are due to dubious experimental techniques; others to compensatory hormonal and enzymatic mechanisms which neutralize the experimentally induced change in the glycemia, especially if this change is of the secondary type and of long standing; some may be genuine.

The role of glucose in the immune response appears to be somewhat analogous to its role in the

possibly through the mediation of the autonomic system³² (Fig. 1).

Normal glycemia, like many other physiologic functions, displays rhythmic oscillations during the 24 hours of the day.²⁹ It varies in a quasi-regular, wave-like fashion between a maximum of some 125 mg. % and a minimum of some 75 mg. %. The wave length of this oscillation is 1-2 hours and its amplitude about 50 mg. %.²⁸ It is possible that a second, seasonal oscillation is superimposed upon it. The amplitude of the normal daily oscillation would be sufficient to induce transitory hypoglycemia or hyperglycemia. Therefore, the existence of the rhythmic oscillations of glycemia could be a factor contributing to the greater susceptibility to infections or to hypersensitivities during the various times of the day or of the year.

Finally, any inflammation that can be influenced by a change in the glycemia must be suspected of having an immunological basis.

SUMMARY

For the purpose of this article, the term "glycemia" means the total amount of sugars in the extracellular

body fluids at the time when an immune response takes place. Evidence is presented in support of the hypothesis that hypoglycemia potentiates the signs and symptoms of hypersensitivity and inhibits those of infection; and that hyperglycemia inhibits the signs and symptoms of hypersensitivity and potentiates those of infection.

The author would like to express his thanks to Dr. and Mrs. P. Sacra for their help in the preparation of this article.

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RÉSUMÉ

Le terme glycémie, employé au cours du présent article, signifie la quantité totale de sucre dans les liquides extracellulaires du corps au moment de la réaction d'immunité.

On a tenté de démontrer que les hypoglycémies aggravent les signes et les symptômes des réactions d'hypersensibilité, et inhibe ceux de l'infection. Les hyperglycémies inhibent les signes et les symptômes des réactions d'hypersensibilité, et aggrave ceux de l'infection.

CANADIAN JOURNAL OF SURGERY

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