Blood Sugar Levels and Allergies

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I SHALL not attempt on this occasion to review the investigations into the relationships between allergies and the metabolism of sugars. Such relationship has often been observed and reported in the past, mostly as incidental additions to other themes; but no systematic study of it appears to have been made.

I shall simply start with the year 1957 when Andres Goth (22) in Dallas, and I (7) in Montreal, observed almost simultaneously, but quite independently, that the dextran-anaphylactoïd reaction in rats depends on the sugar level in their blood. The anaphylactoïd reaction, also called inflammation, and considered as not immunological in nature, was discovered by Professor Hans Selye in 1937 (38). The date of the discovery may now safely be revealed, since the present discourse is a contribution of one of his students to the celebrations of Professor Selye's sixtieth birthday. He introduced the appellation "anaphylactoïd" in honor of his own mentor, Professor A. Biedl from Prague, who together with R. Kraus used that term to describe the peptone shock they observed in dogs (16). Speaking of R. Kraus, it is useful to recall in passing that, in 1897, he also discovered the precipitin reaction between antiserum and antigen (25) considered as a classical example of an immunologic interaction. The anaphylactoïd and immunologic phenomena, having had an almost common historical origin, subsequently led divergent scientific existences. Evidence adduced here points to additional links between them.

Glycemia and the Dextran Anaphylactoïd Reaction in Rats

Anaphylactoïd reactions are produced by a single injection of various substances (24), of which dextran has certain advantages.

TABLE I

EXPERIMENTAL PROCEDURES THAT POTENTIATE OR INHIBIT THE DEXTRAN-ANAPHYLACTOÏD REACTION IN RATS

Potentiation	*Hypoglycemia*	*Reference*	*Inhibition*	*Hyperglycemia*	*Reference*
1. Pretreatment with dextran	?	(9)	1. Antihistaminic drugs	?	(24)
2. Thyroïd hormone administration	?	(39)	2. Inhibitors of 5-hydroxytryptamine	?	(32)
3. Adrenalectomy	Present	(24)	3. Glucocorticoïd-like steroids	Present	(24)
4. Fasting	Present	(1)	4. D-glucose administration	Present	(3)
5. Insulin administration	Present	(7)	5. Alloxan diabetes	Present	(2)
6. Chlorpropamide administration	Present	(39)	6. Certain simple sugars administration	(Present)	(1)
7. Hypoglycemic drugs administration	Present	(6)			

It is a polymer of glucose—the common physiologic sugar—and it is available in a fairly pure chemical form.

West and his collaborators (39) obtained evidence that the reaction of rats to dextran is a genetic trait regulated by a dominant allele. It is a fact that Sprague-Dawley rats and most other strains are susceptible to dextran, but Wistars are less so and the highly inbred Wistar-Furth not at all (21).

Genetics apart, the dextran reaction has been known to be potentiated or inhibited by a number of apparently unrelated procedures listed in Table I. A glance at this Table reveals that procedures resulting in hypoglycemia potentiate the reaction, whereas those resulting in hyperglycemia inhibit it. Not only the hyperglycemia due to an increase of circulating glucose, but indeed hyperconcentration of other mono- and disaccharides displays inhibiting effects (Fig. 1). On the other hand, equimolar amounts of non-sugars are ineffective in general (Fig. 1) (1).

The inhibition by hyperglycemia is ephemeral. It lasts as long as the hyperglycemia and disappears when the excess sugar is eliminated. This can be observed in rats injected simultaneously with dextran (120 mg/Kg, i.v., 6% w/v in saline, Abbott, M. W. $\simeq$ 70,000) and with a hyperglycemic dose of glucose (80 mmol/Kg

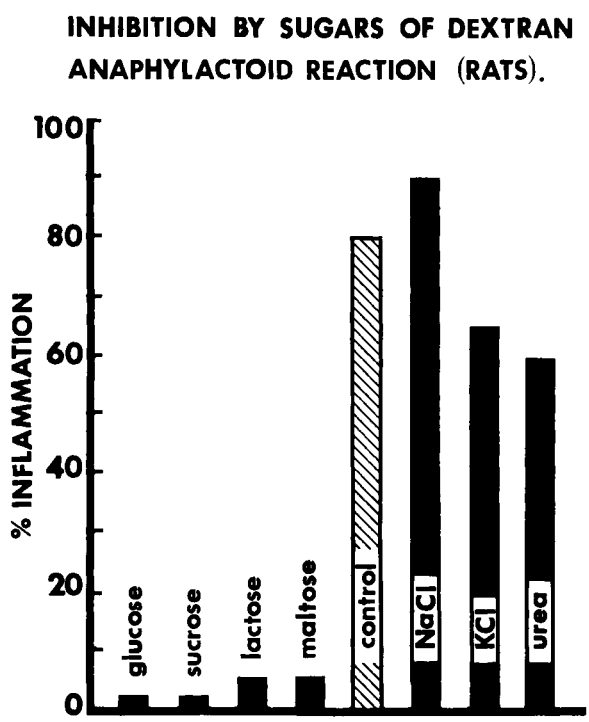


FIGURE 1. Inhibition by sugars of the dextran anaphylactoïd reaction in Sprague-Dawley rats. The severity of anaphylactoïd reaction is expressed as "% inflammation" at 2 hours after injection of 120 mg/Kg dextran, i.v., in normoglycemic rats. All other substances were injected s.c. in equimolar doses. (From: ADAMKIEWICZ, V. W., and P. J. SACRA: *Fed. Proc., 26*:224, 1967.)

per os or s.c.) (3). The animals that should normally react within 60 minutes after the dextran show no sign of reaction for two to three hours and up to ten hours if reinjected with the glucose. Only when the excess sugar has been removed from the circulation, the anaphylactoïd reaction appears quite suddenly. The animals scratch; their nose, ears, paws and ano-genital regions (called target organs) become warm, red, and conspicuously swollen. The same may be shown with alloxan diabetic rats that are refractory to dextran. But within two hours after lowering their blood sugar with insulin they become susceptible again (Fig. 2) (2).

There exists, in fact, an inverse relationship between the inten-

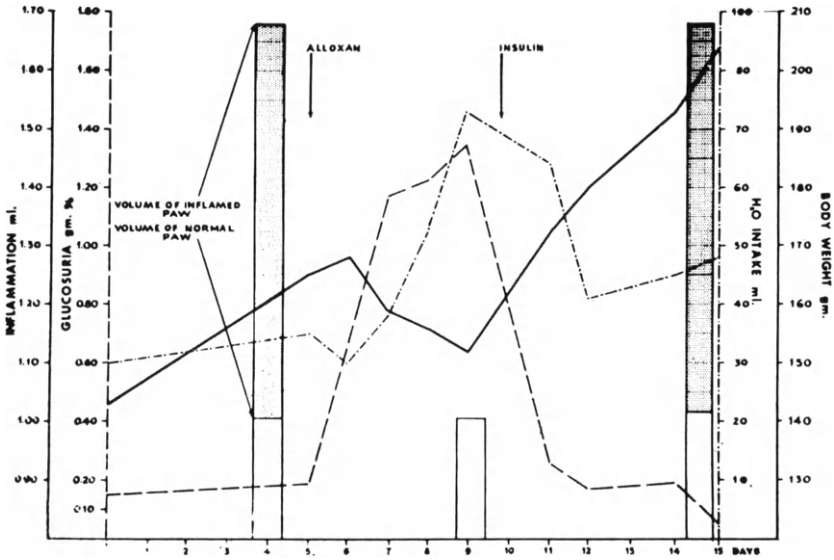


FIGURE 2. Inhibition of the dextran anaphylactoïd reaction by alloxan diabetes, and restoration by insulin therapy. The first four days are a control period. A group of Sprague-Dawley rats that grew normally (——), drank a constant amount of water (-·-·-·) and showed no glucosuria (– – –), underwent a reaction following a systemic injection of dextran, as judged by the increased volume of a swollen hind paw (shaded rectangle). On the fifth day, alloxan was administered *(arrow)* and diabetes developed as judged by body weight, water consumption and glucosuria changes. The paws did not swell following dextran *(open rectangle)*. On the tenth day insulin therapy was started *(arrow)* and the signs of diabetes disappeared. The hind paw became swollen following dextran injection. (From: ADAMKIEWICZ, V. W., and L. M. ADAMKIEWICZ: *Am. J. Physiol., 197*:377, 1959.)

sity of the dextran reaction and the level of blood sugars (Fig. 3). This relationship does not result from some osmotic change in hyperglycemic animals, since changing the osmosis with non-sugars is without effect (3). Neither is it induced by some metabolite of glucose, since subcutaneously injected equimolar doses of sucrose, which is practically non-metabolisable by this route, yield effects similar to glucose (Fig. 1) (1). What appears to occur, therefore, is a competition between the glucose molecules of the dextran and the circulating free sugars for some receptors in the animal (4). These receptors when combined with the dextran

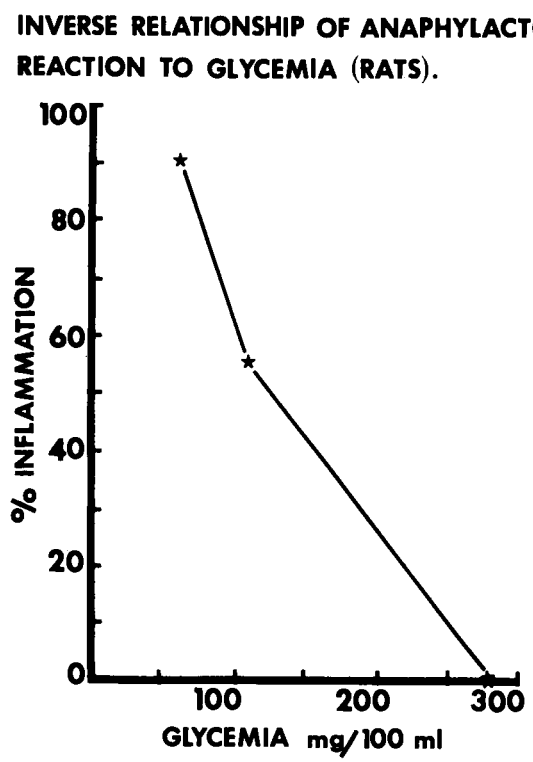


FIGURE 3. The intensity of anaphylactoïd reaction produced in Sprague-Dawley rats by a constant dose of dextran (120 mg/Kg, i.v. M.W. ≃ 70,000) varies inversely with blood sugar levels. (From: ADAMKIEWICZ, V. W., and L. M. ADAMKIEWICZ: *L'Union Méd. du Canada, 94*:1264, 1965.)

trigger the anaphylactoïd reaction. But when saturated with excess free glucose or with excess analogous sugars, they do not react with dextran, thus appearing to display greater avidity for simple sugars than for polysaccharides. Should this be the case, glucose would exert an auto-haptenic-like inhibition with respect to dextran, akin to haptenic inhibitions of classical immunology (4, 5, 28).

Such effects would be surface phenomena subject to the criteria of the physical-chemistry of surfaces. In the case of the dextran-glucose competition for the surface of some receptors, a Langmuir adsorption isotherm may in fact be derived. It can be shown by means of this that the intensity of the dextran reaction should be

inversely proportional to the concentration of glucose in the blood.

Vg = velocity of glucose adsorption.
Vd = velocity of dextran adsorption.
V'g = velocity of glucose desorption.
V'd = velocity of dextran desorption.
Sg = fraction of surface covered with glucose.
Sd = fraction of surface covered with dextran.
Cg = concentration of glucose (blood sugar level).
Cd = concentration of dextran (dose injected).

The fraction of the surface (receptors) covered with glucose and with dextran is: $Sg + Sd = S$.

Therefore, the fraction of the surface that remains free is: $1 - S$.

The speed of adsorption of glucose on the free surface is proportional to: $Vg \simeq (1 - S)\,Cg$.

The speed of adsorption of dextran on the free surface is proportional to: $Vg \simeq (1 - S)\,Cd$.

Adsorption is a reversible process. The glucose and dextran that are adsorbed may also desorb.

Therefore, the speed of desorption of glucose is proportional to:

$$V'g \simeq Sg.$$

The speed of desorption of dextran is proportional to:

$$V'd \simeq Sd.$$

When the speeds of adsorption and desorption of glucose and dextran reach equilibrium we have: $Vg = V'g$ and $Vd = V'd$.

Therefore: $\dfrac{Vg}{Vd} = \dfrac{V'g}{V'd}$

By substituting: $\dfrac{(1 - S)\,Cg}{(1 - S)\,Cd} = \dfrac{Sg}{Sd}$ **and** $\dfrac{Cg}{Cd} = \dfrac{Sg}{Sd}$

It was postulated that the anaphylactoïd reaction is triggered after combination of dextran with the receptors.

Therefore, the intensity of reaction is proportional to: $\simeq Sd$.

Consequently, it is also proportional to: $\simeq Cd$.

And with respect to glucose the intensity of reaction becomes proportional to:

$$\frac{1}{Cg}$$

It is, however, indeed premature to rely too strictly on equations in this system. The Langmuir isotherm, for example, is based on the Law of Mass Action. No proof can be obtained at present that the Law itself applies here (4).

TARIF, The Transferable Anaphylactoïd Reaction Inducing Factor

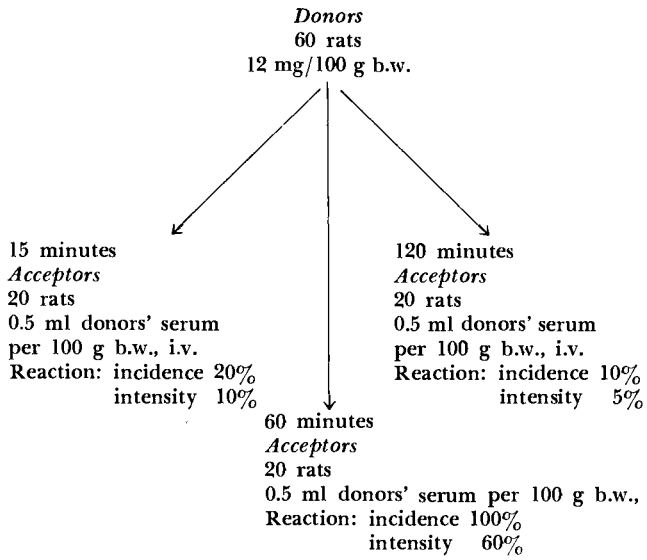
The dextran reaction may be transferred passively from one lot of rats—the Donors—to another lot—the Acceptors. The transfer is possible only during a restricted period of time in the course of the reaction (9). Serum taken about 60 minutes after the injection of dextran into donors (12 mg/100 g, i.v.) and reinjected into the acceptors (0.5 ml/100 g, i.v.) produces in them the same reaction as that seen in the donors, consisting of the conspicuous swelling of the target organs. However, serum taken from the donors at some other time, 15 or 120 minutes after dextran, results in little or no reaction in the acceptors (Table II).

If the donors and the acceptors are made hypoglycemic with insulin (20 u/Kg, s.c., Crystalline-Insulin-Zn, Connaught), the passive transfer may be performed three times, at hourly intervals, from Donors to Acceptors I, then from Acceptors I to Acceptors II, etc. (12). Each successive lot of animals undergoes the anaphylactoïd reaction in turn. However, the incidence and intensity subside progressively to disappear in Acceptors IV (Table III, experiment 1). Only two such transfers are possible with serum from normo-glycemic donors, and only one from hyperglycemic donors, the acceptors being hypoglycemic, throughout (Table III, experiments 2, 3 and 4) (12).

At each of the consecutive transfers, the original serum of donors becomes diluted about 20 times by the extracellular fluids of each acceptor. Let us suppose that the dextran injected into the first donors remains intact in their fluids. The amount present one

TABLE II

PASSIVE TRANSFER OF DEXTRAN-ANAPHYLACTOÏD REACTION IN SPRAGUE-DAWLEY RATS



(From: ADAMKIEWICZ, V. W., and L. M. ADAMKIEWICZ: *L'Union Méd. du Canada, 95:*1155, 1966.)

hour later should then be equal to: $\frac{12 \text{ mg}}{20 \text{ ml}} = 0.6$ mg/ml, in a rat of 100 g body weight, or 0.3 mg in 0.5 ml of transferred serum. After the second transfer the amount injected into Acceptors III would be: $0.3 \text{ mg} \times \frac{0.5 \text{ ml} \times 0.5 \text{ ml}}{20 \text{ ml} \times 20 \text{ ml}} = 0.00018$ mg/100 g, i.v. But, so small a dose of dextran is insufficient to trigger the anaphylactoïd reaction, even in hypoglycemic rats (9). This and other evidence (9, 12) prompted us to postulate that the anaphylactoïd reaction is mediated by a factor, the TARIF. This factor, which could consist of a complex between dextran and a physiologic molecule, is formed in the donor rats within some 60 minutes and induces the anaphylactoïd reaction in them. Upon transfer, it induces the reaction in the acceptors. The factor is destroyed *in vivo* at a rate such that two hours after its formation too little remains for passive transfer into normo-glycemic acceptors. Hypo-

glycemic acceptors, however, are more sensitive to it and may detect it for longer periods of time. On the other hand, when frozen *in vitro* it keeps for weeks.

The production of this factor is inhibited by glucose (12), because rats with low blood sugar levels make more of it than hyperglycemic rats, three consecutive transfers being possible with the

TABLE III

GLYCEMIC STATES AND THE CONSECUTIVE PASSIVE TRANSFERS OF ANAPHYLACTOID-REACTION-INDUCING FACTOR

	*Donors**	*Acceptors* I*	*Acceptors* II*	*Acceptors* III*	*Acceptors* IV*
Experiment 1: Hypoglycemic donors to hypoglycemic acceptors.					
Glycemia mg/100 ml	55 ± 4	65 ± 3	62 ± 3	62 ± 3	60 ± 2
Anaphylactoïd Reaction:					
Incidence %	100	100	66	16	0
Intensity %	70	56	32	5	0
Experiment 2: Normoglycemic donors to hypoglycemic acceptors.					
Glycemia mg/100 ml	116 ± 4	60 ± 2	60 ± 2	60 ± 2	–
Anaphylactoïd Reaction:					
Incidence %	100	100	83	0	–
Intensity %	45	65	34	0	–
Experiment 3: Hyperglycemic (glucose) donors to hypoglycemic acceptors.					
Glycemia mg/100 ml	216 ± 15	64 ± 3	64 ± 3	–	–
Anaphylactoïd Reaction:					
Incidence %	66	83	0	–	–
Intensity %	29	42	0	–	–
Experiment 4: Hyperglycemic (diabetic) donors to hypoglycemic acceptors.					
Glycemia mg/100 ml	437 ± 57	55 ± 4	55 ± 4	–	–
Anaphylactoïd Reaction:					
Incidence %	0	83	0	–	–
Intensity %	0	53	0	–	–
Experiment 5: Hypoglycemic donors to hyperglycemic (glucose) acceptors I, to hypoglycemic acceptors II.					
Glycemia mg/100 ml	55 ± 4	195 ± 7	55 ± 7	61 ± 5	–
Anaphylactoïd Reaction:					
Incidence %	100	33	83	0	–
Intensity %	67	12	37	0	–
Experiment 6: Hypoglycemic donors to hyperglycemic (diabetic) acceptors I, to hypoglycemic acceptors II.					
Glycemia mg/100 ml	61 ± 2	486 ± 28	55 ± 3	55 ± 3	–
Anaphylactoïd Reaction:					
Incidence %	100	0	66	0	–
Intensity %	70	0	27	0	–

* Six rats per group.

(From: ADAMKIEWICZ, V. W., and P. J. SACRA: *Can. J. Physiol. Pharmacol., 44*:615, 1966. Reproduced by permission of the National Research Council of Canada.)

serum of the former and only one with that of the latter (Table II, experiments 1, 2 and 3). The allergic-like effect of this factor also depends on blood sugar levels, since the injection of TARIF-containing serum into hyperglycemic Acceptors I does not result in anaphylactoïd reaction, but reinjection of the serum from such non-responding Acceptors I into a new lot of Acceptors II that are hypoglycemic leads to a reappearance of the reaction (Table III, experiments 4 and 6) (12). Glucose therefore appears to be involved at both ends of the life-cycle of TARIF. It inhibits its production in the donors, probably by an autohaptenic-like effect. It inhibits the anaphylactoïd reaction TARIF produces at the other end in the acceptors, by a mechanism whose elucidation must await further knowledge of TARIF's structure. At any rate, this last inhibition is a reversible process as shown by experiments 4 and 6 of Table III.

It has been suggested by some investigators that TARIF may be identical with free dextran (26, 27). However, in their experiments, the strain of rats and other conditions differed from those reported above, and no attempt was made at more than one consecutive passive transfer. On the other hand, Polushkin (33), using the Prausnitz-Küstner test, demonstrated the presence of a reagin-type antibody against egg-white in the serum of albino rats. Such rats, when injected with a single dose of egg-white, undergo an anaphylactoïd reaction undistinguishable from that induced by dextran.

Anaphylactoïd reactions have not been considered truly immunological and have been classed together with certain other hypersensitivities under the heading of "non-immunological equivalents of hypersensitivity reactions" (17). The reason is mainly that they do not require pre-sensitization and are not accompanied by the presence of identifiable antibodies. However, several of the anaphylactoïd agents do probably react with pre-existing "natural antibody" (33) and elicit a conventional immune response. Furthermore, complement-containing guinea-pig serum potentiates the dextran anaphylactoïd reaction (8) while the inhibiting effect of hyperglycemia may also be reproduced in the following classical immunological situations.

Anaphylaxis and Immune Hemolytic Anemia

Normal rats and mice are resistant to horse-serum or egg-white anaphylactic shock. It is, however, sufficient to lower the blood sugar levels of these animals (insulin, or 24-hour fast) to obtain high anaphylactic mortality and an exacerbation of the specific anaphylactic lesions in the gut and elsewhere (13). Should the hypoglycemic state be neutralized by administrations of glucose, the animals regain their original resistance and the anaphylactic lesions subside (Table IV). An inverse relationship occurs in mice between the intensity of the shock and the blood sugar levels (Fig. 4), similar to that for the dextran reaction in rats (Fig. 3). In the case of anaphylaxis, the change of the glycemic status is brought about at a time when antibody production is fully completed. Therefore, the inhibitory effect of the blood sugars

TABLE IV

AGGRAVATION OF THE ANAPHYLACTIC SHOCK IN THE RAT BY HYPOGLYCEMIC STATES

Experiment, Group and Treatment	*Number of Rats*	*% Mortality*	*Number of Rats*	*Intensity of Lesion in the Ileum*
Experiment 1—Horse-serum anaphylactic shock				
G I, normo-glycemic controls	20	0	10	1.84 ± 0.16
G II, fasting hypoglycemic state	20	50	10	2.37 ± 0.24
G III, fasting hypoglycemic state neutralized with glucose	20	0	10	1.65 ± 0.26
G IV, hyperglycemic with glucose	20	0	10	1.05 ± 0.18
Experiment 2—Horse-serum anaphylactic shock				
G II, insulin hypoglycemic state	20	40	10	2.40 ± 0.29
G III, insulin hypoglycemic state neutralized with glucose	20	0	10	1.87 ± 0.17
Experiment 3—Egg-white anaphylactic shock				
G I, this is a control group that was not sensitized but which was in an insulin hypoglycemic state, and challenged	20	0	–	–
G II, normo-glycemic controls	20	0	–	–
G III, insulin hypoglycemic state	20	60	–	–
G IV, insulin hypoglycemic state neutralized with glucose	20	0	–	–

(From: ADAMKIEWICZ, V. W., P. J. SACRA, and J. VENTURA: *J. Immunol., 92*:3, 1964.)

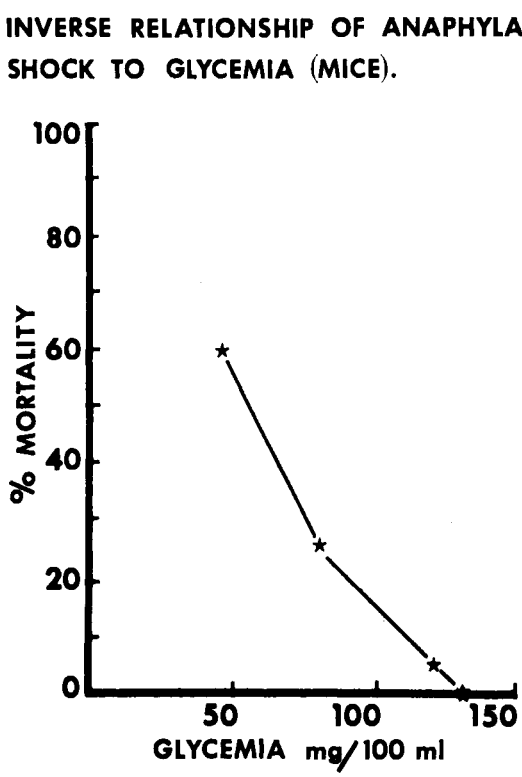


FIGURE 4. The intensity (% mortality) of anaphylactic shock produced by a constant dose of horse-serum in mice varies inversely with blood sugar levels. (From: ADAMKIEWICZ, V. W., and L. M. ADAMKIEWICZ: *L'Union Méd. du Canada, 94*:1264, 1965.)

must alter the antigen-antibody complex formation or its sequel. Sanyal *et al.* (36) reported that lowering the blood sugar with insulin in rats had no effect on subsequent "in vitro anaphylaxis" (Shultz-Dale reaction). This would suggest that the inhibiting effect of blood sugar occurs in the circulation.

Similar observations may be made in mice and rats with hemolytic anemia, following inoculation with specific rabbit anti-erythrocyte sera (14). The dose of hemolytic antiserum required to produce an LD_{50} in mice (within 24 hours) increases directly with the blood sugar levels obtaining at the time of inoculation. Conversely, the mortality following a fixed dose of antiserum is

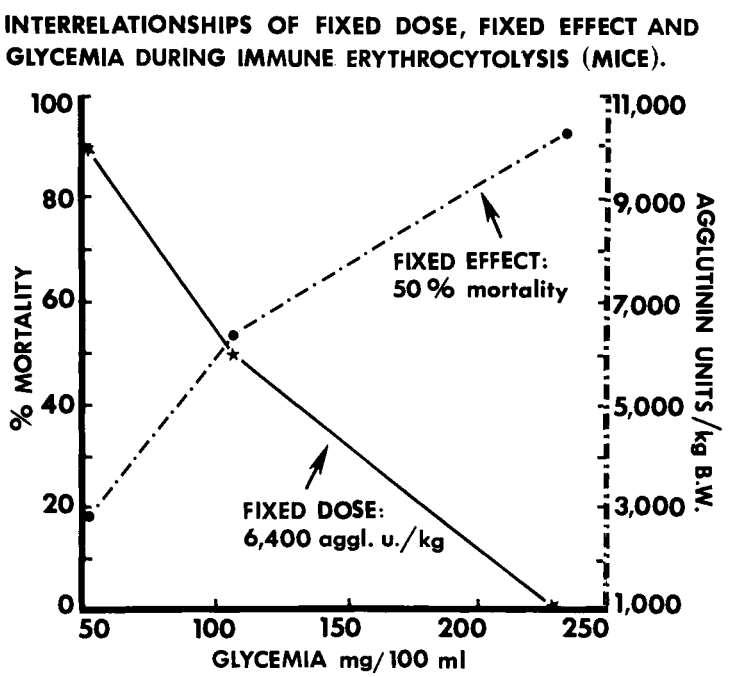


FIGURE 5. The intensity (% mortality) of immune hemolytic anemia (——) produced in mice by a constant dose of rabbit antimouse erythrocyte serum varies inversely with blood sugar levels. But the dose of antiserum required to produce a constant effect (-·—·—·) varies directly with the blood sugar level.

in inverse relationship to the blood sugar levels (Fig. 5). Furthermore, a small dose of antiserum (1,000 agglutinin units/Kg, i.p.) produces little or no mortality in hypoglycemic mice, but the resulting anemia is severe and protracted (10 days). The erythrocyte count falls from the normal of $9 \times 10^9/ml^3$ to about $4 \times 10^9/ml^3$. On the other hand, the same small dose in hyperglycemic mice results in mild anemia (8×10^9 erythrocytes/ml^3) of short duration (2 days), (11, 14), (Fig. 6).

In the case of immune hemolytic anemia, unlike in the anaphylactoïd and anaphylactic reactions, an upper limit for blood sugar is reached beyond which no further protection occurs (11, 14). This happens in the mouse at some 225 mg glucose/100 ml. Such hyperglycemia still inhibits a dose of antiserum equal to 10,200 agglutinin units/Kg, but higher doses are fully effective inde-

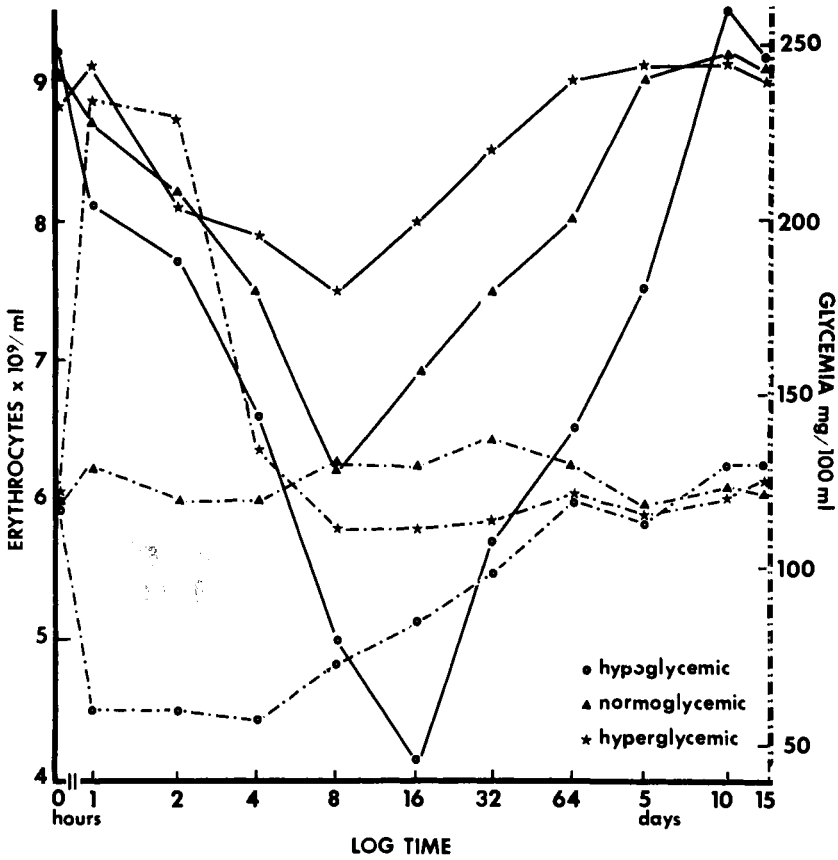


FIGURE 6. Patterns of hemolytic anemia produced by a fixed dose of rabbit antimouse erythrocyte serum, in hypo- (○), normo- (△) and hyperglycemic (*) mice. Blood sugar levels (–·–·–·) were measured at intervals before and after the glycemic state was changed by insulin or glucose administration at 1 hour. At that time, antiserum was also injected. Note that the number of erythrocytes (———) decreases most markedly and recovery is slowest in the hypoglycemic mice. (From: ADAMKIEWICZ, V. W., and P. J. SACRA: *Fed. Proc., 26*:224, 1967.)

pendently of any blood sugar levels. It thus appears that the number and kinds of receptors that react with the hemolytic antiserum, or with some product of the antigen-antibody reaction, are large. High doses of anti-serum find enough receptors to react with under any circumstances. But, in anaphylactoïd and anaphy-

lactic reactions, the number and kinds of the receptors are limited. They become totally unavailable in hyperglycemia.

Various mechanisms could be postulated to explain the inhibition of immune hemolytic anemia in the presence of sugar in the blood *in vivo*. Some mechanisms would require a direct participation of glucose, others the participation of different molecules whose concentration in the blood would be synchronized to the sugar levels. The hemolytic antiserum, of course, hemolyses and agglutinates erythrocytes also *in vitro,* and provides a convenient means for the study of these reactions. However, neither hemolysis nor agglutination of washed rat-erythrocytes is modified by an *in vitro* incubation with the specific antiserum mixed with complement and with various concentrations of glucose (0 to 200 mg/100 ml), (Fig. 9), (11). The dynamics of hemolysis of whole blood taken from hypoglycemic rats and subsequently incubated *in vitro* with antiserum and complement to which various glucose concentrations have been added also remains unaltered (Fig. 7). Glucose, therefore, does not appear to directly inhibit the hemolytic anemia.

The amount of circulating endogenous insulin is synchronized to the blood sugar levels. However, this hormone is unlikely to be involved in the inhibition, because rats and mice overdosed with it so as to become hypoglycemic are as sensitive to the hemolytic antiserum as are the fasted hypoglycemic animals that have low insulin levels.

As in the case of dextran reaction, the inhibitory effect of the hyperglycemic state on immune hemolytic anemia is ephemeral. This may be observed in rats given glucose per os from whom samples of blood are taken at hourly intervals thereafter. The speed of hemolysis is then measured in the samples *in vitro* by addition of antiserum and complement. Sugar levels are simultaneously determined. About one hour after the *in vivo* hyperglycemic peak is reached the speed of the *in vitro* hemolysis slows down considerably. Six hours later as hyperglycemia subsides normal speed tends to resume (Fig. 8). Although the inhibitory effect of hyperglycemic blood is transitory, the resultant neutralization of antiserum is permanent. This is seen in agglutinin hyperglycemic mice injected with the small dose of antiserum

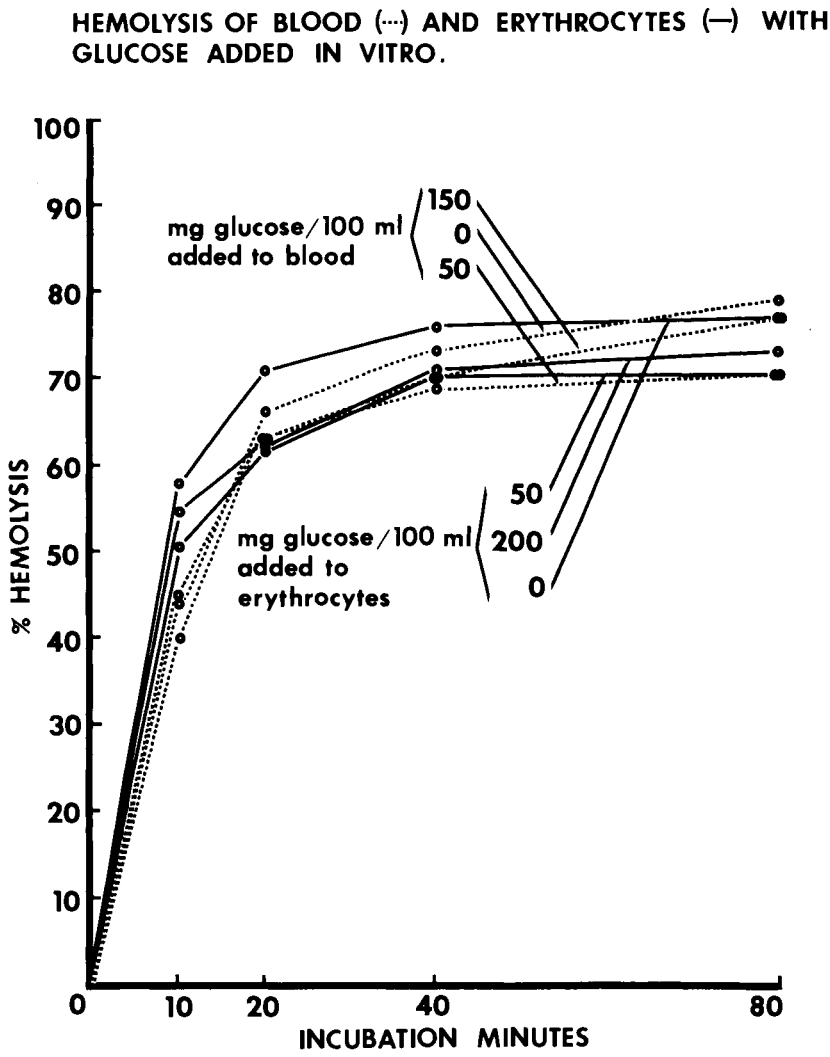


FIGURE 7. In vitro dynamics of immune hemolysis of blood (.....) and erythrocytes (——), following addition of rabbit anti-rat erythrocyte serum, complement, and various concentrations of glucose. Blood and erythrocytes were obtained from insulin-hypoglycemic rats. Note similarity of hemolysis curves despite variations in the amounts of glucose added.

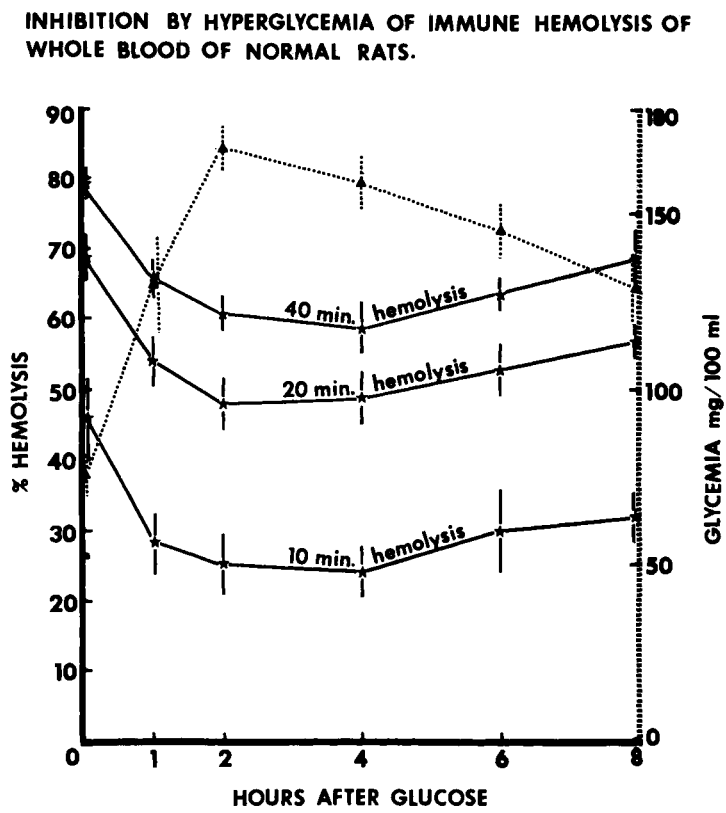


FIGURE 8. Transitory inhibition by hyperglycemia (.....) of the speed of hemolysis of whole blood (——) of rats. At 0 hours, 80 mmol glucose/Kg was administered per os. Samples of whole blood were taken at the 0 hours and at hourly intervals thereafter for 8 hours. The speed of hemolysis in samples was determined by addition of rabbit anti-rat erythrocyte serum and complement *in vitro*. The value of hemolysis was determined after incubations of 10, 20, and 40 minutes. Note that hemolysis is inhibited about 2 hours after glucose administration, irrespective of the length of subsequent incubation. The inhibition corresponds to peak hyperglycemia. Inhibition and hyperglycemia decrease at 8 hours.

(1,000 units/Kg) referred to before (Fig. 6), (14). Blood sugar returns to normal levels within six hours in these mice but the activity of antiserum remains permanently inhibited as judged by the low grade and short duration of the resulting anemia. The dynamics of *in vitro* hemolysis of whole blood depends on whether

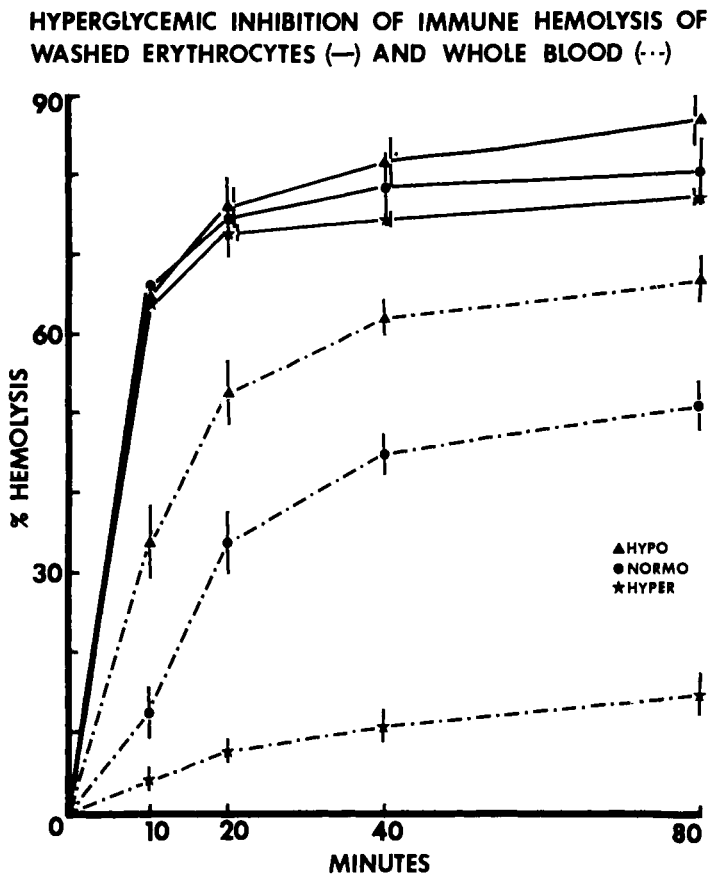


FIGURE 9. Dynamics of *in vitro* immune hemolysis following addition of rabbit anti-rat erythrocyte serum and complement to washed rat-erythrocytes or to whole rat blood. The washed erythrocytes (——) were obtained from hypo- (△), normo- (○) or hyperglycemic (*) rats. No significant difference in the speed of hemolysis is noted. However, the speed of hemolysis of whole blood (–·–·–·) from hypoglycemic rats is much faster than in hyperglycemic animals. The erythrocytes and whole blood were obtained at the second hour after administration of insulin or glucose.

the blood originates from hypo-, normo- or hyperglycemic animals (not to be confused with the unchanging pattern of hemolysis of whole blood to which various concentrations of glucose have been added *in vitro*). Whole blood from hyperglycemic animals hemolyses several times more slowly than whole blood from

hypoglycemic rats (Fig. 9). However, washed erythrocytes hemolyse at the same speed independently of their hypo- or hyperglycemic origin (Fig. 9).

It seems clear then that hyperglycemic whole blood contains a transient excess or lack of something that is directly involved in hemolysis. As pointed out already, glucose and insulin are not "it." Could it be the complement: *in vitro* incubation of complement-containing hemolysing systems with various concentrations of glucose does not affect the dynamics of hemolysis. However, these experiments were conducted in an excess of complement and do not exclude the possibility that the concentration of circulating complement *in vivo* is synchronized to blood sugar levels.

Although the effects of various glycemic states on immune hemolysis are quite striking, we failed to demonstrate any such effect on the agglutination reaction using various experimental set-ups.

Histamine and Compound 48-80

Drugs that inhibit immune reactions display multivalent effects. The antagonists of purine, pyrimidine, folic acid, and especially the alkylating agents, modify fairly specifically any one of the following immunological events: the antibody induction period, primary and anamnestic productions, tolerance and delayed hypersensitivity (37). They also display anti-inflammatory activity against non-specific as well as against the specific immune inflammations that result from delayed or immediate hypersensitivity (37). Somewhat analogous is the multivalent anti-allergic effect triggered by the presence of glucose in blood. This presence inhibits TARIF production as well as its allergic-like action. It interferes with the antigen-antibody combination or its sequel in anaphylaxis and in experimental immune anemia. The presence of glucose in blood also triggers an anti-inflammatory activity.

Endogenous histamine released in immediate hypersensitivity is partly responsible for the subsequent inflammatory changes. It may be demonstrated that the activity of exogenous histamine depends on blood sugar levels. Rats are injected intravenously with Evans blue and by stomach tube with a hyperglycemic dose of glucose (80 mmol/Kg). Every hour thereafter, a "spot test"

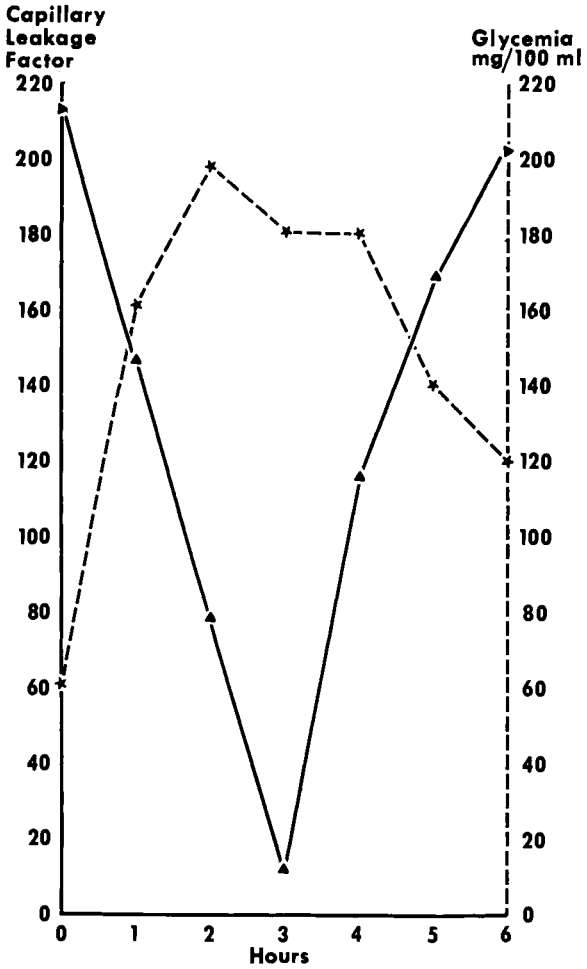


FIGURE 10. Time relationship between blood sugar levels (---) and the capillary leakage (——) in the skin as induced by histamine in rats. 80 mmols glucose/Kg were administered per os. At hourly intervals thereafter, blood sugar levels were determined and a histamine "spot test" was performed in the skin. At the third hour, when hyperglycemia was at a peak, topical injection of histamine (0.02 micromols) induced practically no capillary leakage. (From: ADAMKIEWICZ, V. W., and P. J. SACRA: *Can. J. Physiol. Pharmacol., 43*:877, 1965. Reproduced by permission of the National Research Council of Canada.)

is performed by intradermal injection of 0.02 micromols of histamine in 0.05 ml solution (10). This dose equals about twice the physiological concentration of skin-histamine, and induces capillary leakage. The blue-colored plasma seeps out and a colored spot forms, the dimensions of which may be measured. The size of this spot becomes smaller as the blood sugar levels increase in the rat. One hour after the peak hyperglycemia is reached (three hours after sugar administration) practically no leakage occurs around the histamine (Fig. 10). As hyperglycemia subsides, the spot reappears and is again full size six hours after sugar administration. The transient inhibition by hyperglycemia in this experiment is identical with that of the dextran-reaction and of the hemolytic anemia.

The specificity of this inhibition may further be studied in normo-glycemic, Evans-blue injected rats treated intradermally with 0.01 to 0.02 micromols of histamine mixed with serial dilutions of glucose, or other simple sugars and control substances (10). The optimal inhibitory molar ratio of glucose to histamine is 16:1. Higher or lower molar ratios, as well as equimolar control substances, do not inhibit the histamine. Various other simple sugars display specific although distinct optimal inhibitory molar ratios (Table V).

Goth *et al.* showed both *in vivo* (22) and *in vitro* (20) that glucose inhibits the endogenous histamine release resulting from the interaction of dextran with tissues. Beraldo *et al.* (15) and Poyser and West (34), using the "spot test," produced capillary leakage by intradermal injection of dextran (15, 34), yeast mannan (34), ovomucoid (34), and zymosan (34). The leakage was inhibited by diabetes (15) and by mixing the polysaccharides with certain simple sugars (34) that were either identical with those of the polysaccharides or were related to them by common stereochemical features, and would thus be expected to exert a haptenic inhibition (28). However, endogenous histamine was also involved in the capillary leakage induced by the topical polysaccharides, since antihistaminics were inhibitory (34). Glucose and the other simple sugars, besides acting as inhibitory haptens towards the respective polysaccharides, could also therefore inhibit more directly the histamine action, as described in the paragraph above,

TABLE V

OPTIMAL MOLAR RATIOS OF TOPICAL SUGARS THAT INHIBIT CAPILLARY LEAKAGE FOLLOWING INTRADERMAL DEPOSITION OF 0.01 μMOL HISTAMINE (RESULTS EXPRESSED AS "LEAKAGE FACTOR")

μmols of sugar, or control substance, added to 0.01 μmol of histamine	0 (Saline control)	0 (Histamine control)	0.005	0.01	0.02	0.04	0.08	0.16	0.32	0.64	1.28
					CAPILLARY LEAKAGE FACTOR						
Saline control	17 ± 5	–	–	–	–	–	–	–	–	–	–
D-Glucose	–	300 ± 12	–	–	–	262	144 ± 10*	60 ± 10*	170 ± 10*	–	257
D-Arabinose	–	206 ± 7	–	–	156	157	199	102 ± 10*	52 ± 10*	121 ± 9*	188
L-Arabinose	–	206 ± 7	–	–	187	164	190	103 ± 16*	57 ± 13*	116 ± 9*	152
L-Xylose	–	206 ± 7	–	–	196	170	123 ± 17*	180	198	165	175
Sucrose	–	206 ± 7	196	120 ± 11*	73 ± 6*	99 ± 6*	150 ± 8	171	205	218	210
Urea	–	250	250	243	197	244	228	–	244	–	–
NaCl	–	200	206	182	199	180	240	195	206	–	–
Molar ratio of sugar (or control substance) to histamine	0 : 0	0 : 1	0.5 : 1	1 : 1	2 : 1	4 : 1	8 : 1	16 : 1	32 : 1	64 : 1	128 : 1

* These values are statistically different from the histamine control, $p < 0.001$.

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the two inhibitions resulting in the over-all decrease of capillary leakage.

Instead of by polysaccharides, endogenous histamine may be discharged by compound 48-80, a synthetic polymer containing trimeric formaldehyde. This compound injected into rats produces a reaction analogous to the dextran inflammation, discharges endogenous histamine, a lipase (23) and other toxic substances. In sufficient doses, it causes death. The LD_{50} of this drug is directly related to the blood sugar levels obtaining at the time of injection (35). In hyperglycemic rats, the LD_{50} (7.3 mg/Kg) is six times higher than in hypoglycemic animals (1.22 mg/Kg). Conversely, a fixed dose of the drug produces mortality effects that vary inversely with the blood sugar levels (Fig. 11). These relationships are analogous to what was stated for the dextran anaphylactoïd reaction, for anaphylaxis, and especially for

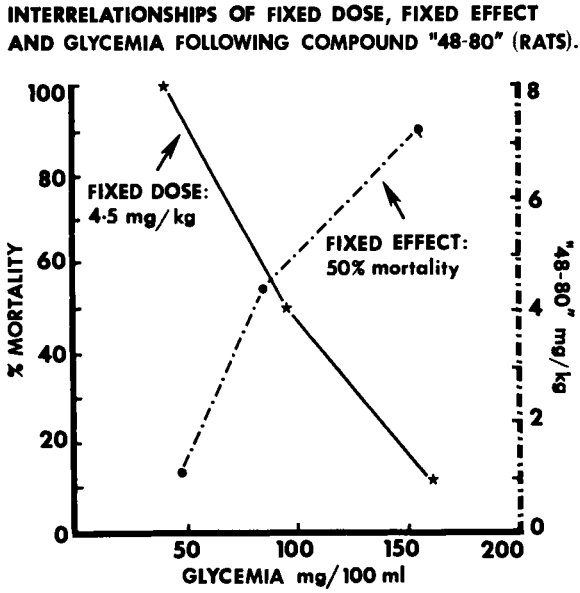

FIGURE 11. The mortality of rats (——) following a fixed dose of compound 48-80 varies inversely with blood sugar levels. But the dose of compound 48-80 necessary to produce a constant mortality (-·-·-·) increases with the blood sugar levels. (From: ADAMKIEWICZ, V. W., and P. J. SACRA: *Fed. Proc.*, *26*:224, 1967.)

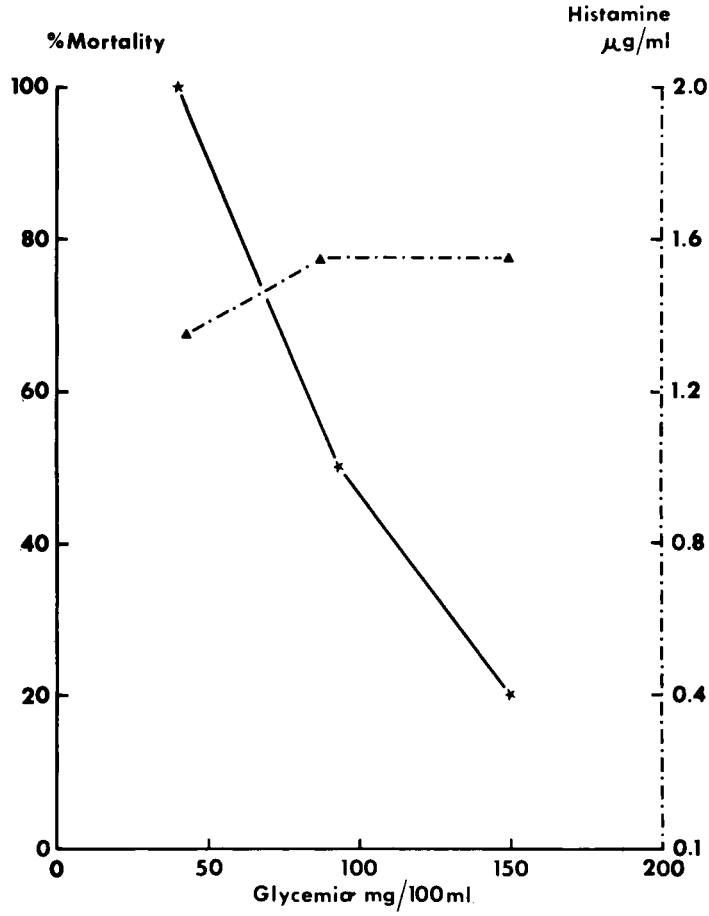

FIGURE 12. The mortality of rats (——) following a fixed dose of compound 48-80 varies in an inverse relationship with the blood sugar levels. But the amount of endogenous histamine (–·–·–) liberated by the fixed dose is independent of glycemia variations. (From: ADAMKIEWICZ, V. W., and L. M. ADAMKIEWICZ: *L'Union Méd. du Canada, 94:*1264, 1965.)

hemolytic anemia (Fig. 5). Although higher blood sugars inhibit the lethal effect of 48-80, they do not change the amount of endogenous histamine the drug discharges (19, 22, 35), (Fig. 12). One would be tempted to assume, therefore, that glucose protects against the lethal action of compound 48-80 by inhibiting the toxicity of the endogenous histamine the compound liberates. This is unlikely,

however, because the LD_{50} of exogenous histamine is unaffected by blood sugar variations. It must be assumed, therefore, that the protection by glucose against the toxicity of 48-80 results either from interference with some reaction between the drug and a receptor or from interference with the lethal action of a substance, other than histamine, but liberated by the drug. The same reasoning also applies to the inhibition by glucose of the lethal effect of anaphylaxis.

The Oscillations of Blood Sugars and Susceptibility to Allergy

Blood sugar levels of normal animals, like any other physiological function, oscillate around a base-line. The wave length of this oscillation in man is about 2 to 4 hours and the amplitude about 40 mg glucose/100 ml (31). Similar oscillations have long been noted in animals after stoppage of a glucose infusion. Normal mice

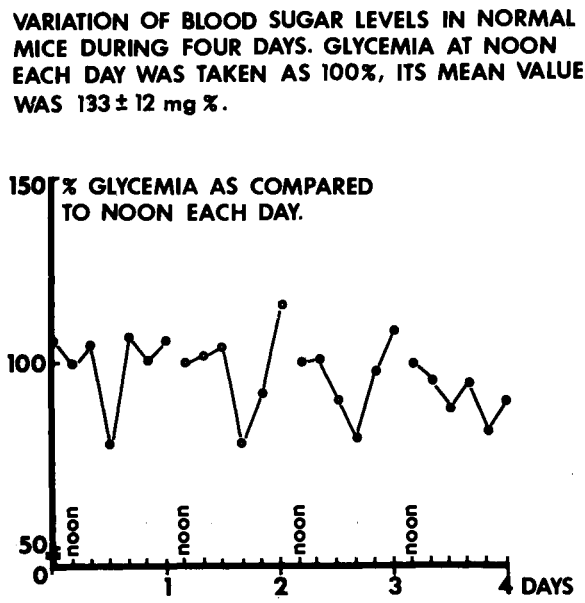

FIGURE 13. Diurnal variations of blood sugar levels of normal mice fed ad libitum during four 24-hour periods. The blood sugar level at noon each day was taken as 100%. Each point represents average value from ten mice. Note that normal mice go through a "spontaneous" hypoglycemic period between 8 and 12 p.m. each day.

display a blood sugar oscillation that hints at the existence of a circadian rhythm (Fig. 13). The hypoglycemic phase lasts from 8 to 12 p.m., and coincides with the night-feeding period of these nocturnal animals. The difference between the hypo- and hyperphases may reach as high as 50 mg/100 ml.

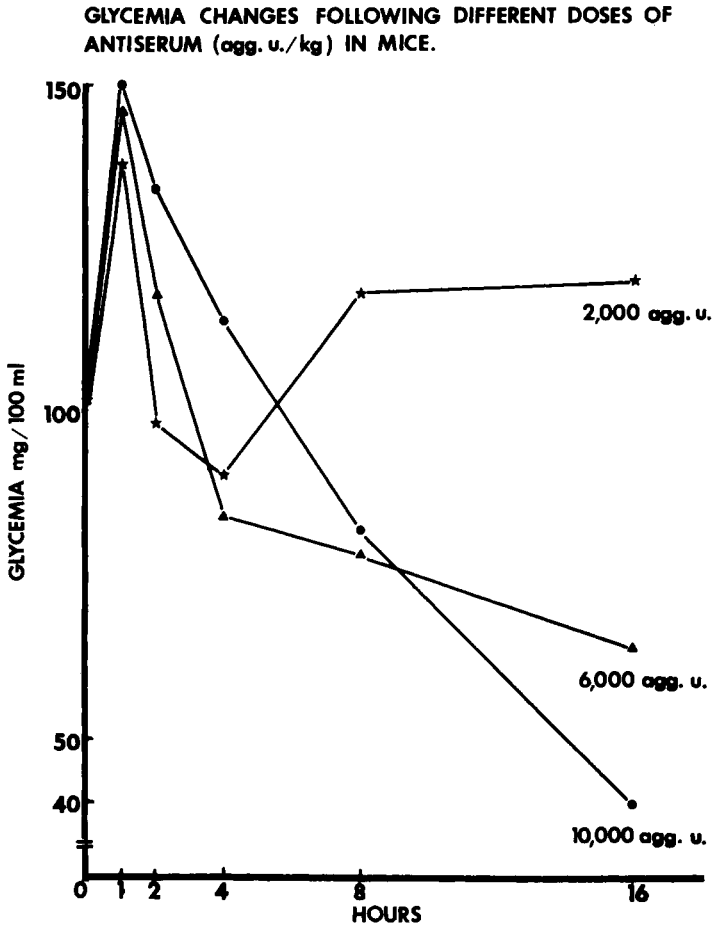

FIGURE 14. Biphasic blood sugar level variation in mice injected with rabbit antimouse erythrocyte serum. Following each dose of antiserum, the first phase is a hyperglycemia that returns to normoglycemia at about the fifth hour. The second phase is a hypoglycemia when the dose of antiserum is 6,000 agglutinin units/Kg, or more. This is followed by death. With smaller doses of antiserum, the second phase is a normo- or secondary hyperglycemia accompanied by survival of the mice.

The susceptibility to small doses of certain allergens or antigens may conceivably depend, therefore, on whether the animals are in their hypo- or hyperglycemic phase. In turn, the differential susceptibility would become critical in the evaluation of clinical and other tests that make use of small amounts of such antigenic material. Long (29), for example, suggested that the tuberculin reaction is related to the glycemic state.

On the other hand the ability of animals to raise blood sugar levels by up to 50% may serve as a first-line defense against certain invading allergens or antigens. Mikami, in 1925 (30), noticed that rabbits overdosed with diphtheria toxin undergo a biphasic change in blood sugar levels. An initial hyperglycemia is followed by secondary hypoglycemia and death within 24 hours.

A similar biphasic change is seen in mice injected with hemolytic antiserum (Fig. 14). The primary phase is a hyperglycemia that is independent of the dose of antiserum injected. It reaches a peak some two hours after inoculation and returns to normal some three hours later. This may be interpreted as an attempt on the part of the animal at neutralization of the antiserum or of some product of antigen-antibody reaction, since hyperglycemic mice and rats tolerate doses of certain antigens or allergens several times higher than normo-, or hypoglycemic mice. On the other hand, the secondary phase depends on the initial dose of antiserum. Thus, larger doses that lead to mortalities produce secondary hypoglycemia. The cause of this is not known, although it could result in part from the anorexia of the animals overdosed with the antiserum or, in the case of the Mikami experiment, with diphtheria toxin. However, it is intriguing that after a small initial dose of antiserum the secondary phase is not a hypoglycemia but a normo- or hyperglycemia, and this is followed by the survival of the animals (Fig. 14).

Conclusions

For some time, studies in immunology have centered on antigens, antibodies, and their interaction, to the detriment of other physiological aspects, although early investigators, R. Kraus for example, set their sights on the response of the entire animal in an immunological situation.

Physiological glucose, an ubiquitous and active molecule, obviously modifies, directly or indirectly, the course of anaphylaxis, immune hemolytic anemia, immune hemolysis, as well as the sensitivities to polysaccharides, histamine, and drugs such as compound 48-80. Admittedly, the influence of glucose is not very marked when the dose of the antigenic or allergenic material that invades the "milieu intérieur" is large. However, massive invasion is rare. The common occurrence, rather, is a constant invasion by minute amounts of such material. Physiological processes engaged in the neutralization of this material constitute what is known in immunology as "natural resistance" (18).

"Natural resistance" is defined as "non-specific resistance determined by physiological conditions subject to variation from one animal to another and within a single individual at different times" (18). Thus defined, it comprises physical and chemical barriers presented by the epithelium, age, state of nutrition, as well as the several antibacterial substances of normal body fluids and tissues (properdin, phagocytin, lysozyme, etc.) and intermediates of immune reactions such as the complements.

This is indeed a heterologous group of phenomena in need of clarification. I think the anti-allergic effect of physiological glucose belongs in this group. It is significant that glucose as a factor of "natural resistance" makes all the difference between the survival and death of an animal subjected to the experimental conditions described herein.

Abstract

Increasing the blood sugar from the hypoglycemic level of 50 mg/100 ml to the hyperglycemic value of 250 mg/100 ml inhibits or suppresses the following allergic and analogous reactions in rats and mice: 1) anaphylactoïd inflammation; 2) anaphylaxis; 3) experimental immune hemolytic anemia; 4) immune hemolysis; 5) the toxicity of histamine and of compound 48-80.

The anaphylactoïd reaction of rats to dextran may be transferred passively. It is mediated by a blood factor, the production and anaphylactoïd action of which are both inhibited by glucose in the blood.

The following mechanisms are postulated for the multivalent anti-allergic effect of the hyperglycemic state: 1) autohaptenic inhibition by glucose of isologous or homologous polysaccharidic allergens; 2) general interference by glucose in antigen-antibody reactions or their sequels *in vivo;* 3) interference in these reactions by unidentified factors whose level in the blood is synchronized to blood sugar levels.

The anti-allergic effect of the hyperglycemic state is part of the natural immunological resistance.

Abrégé

L'élévation de la glycémie à partir de sa valeur hypoglycémique de 50 mg/100 ml vers une valeur hyperglycémique de 250 mg/100 ml s'accompagne d'une inhibition ou d'une suppression des réactions allergiques, ainsi que de quelques réactions analogues suivantes chez le rat et la souris: 1) l'inflammation anaphylactoïde, 2) l'anaphylaxie, 3) l'anémie hémolitique immune, 4) l'hémolyse immune, 5) la toxicité de l'histamine et du composé 48-80.

L'inflammation anaphylactoïde au dextran chez le rat se prête à un transfert passif. Elle est causée par un facteur sanguin dont la formation ainsi que l'action anaphylactoïde sont toutes deux inhibées par le glucose sanguin.

Les mécanismes suivants sont proposés pour expliquer l'effet anti-allergique multivalent de l'état hyperglycémique: 1) inhibition autohapténique par le glucose d'allergène polysaccharidique iso- et homologue, 2) interférence plus générale du glucose dans l'interaction antigène-anticorps et dans les réactions qui suivent cette interaction *in vivo,* 3) interférence dans ces réactions par des facteurs encore non identifiés dont le niveau sanguin serait synchronisé à la valeur de la glycémie.

L'effet antiallergique de l'état hyperglycémique fait partie de la "Résistance immunologique naturelle."

Acknowledgements

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Addendum

The term allergy (literally: altered energy) as used originally by von Pirquet in 1906 signified an altered capacity for reaction, particularly but not exclusively in relation to immune responses. It is used here in its broad original meaning and encompasses hypersensitivity reactions as well as the "non-immunological equivalents of hypersensitivity reactions" (20).

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R. Veilleux: I should like to congratulate Doctor Adamkiewicz for his very good presentation. His studies have undoubtedly provided anaphylactoid inflammation with a new and hitherto unsuspected dimension. So I am personally very happy to have had this opportunity of hearing the present summary of his work.

My own interest in anaphylactoid inflammation goes back to the years 1961 to 1963. This was the time when Doctor Selye had just developed an experimental system through which it had become possible to calcify, at will, practically any organ or part of the body of the rat (Selye, H.: *Calciphylaxis,* University of Chicago Press, Chicago, 1962). This led to the development of many different syn-

dromes, one of which is characterized by selective calcification of the lips and forelegs of the rat after the administration of certain metallic compounds (Selye, H., *et al.: Brit. Med. J., ii*:1194, 1961). I demonstrated, at that time, that this characteristic localization of calcium was conditioned by the previous occurrence of an anaphylactoid inflammation (Veilleux, R.: *Rev. Can. Biol., 22*:15, 1963) that was, in fact, elicited by the dextrin fraction (Veilleux, R.: *Brit. J. Pharmacol., 21*:235, 1963) of the compound injected. This shed further light on the role played by the metallic fraction of the injected substance, namely iron, which I then considered as the seeder or primer of the calcium deposition (Veilleux, R.: *Thèse,* Université de Montréal, 1963; *Acta Histochem., 17*:343, 1964). At the same time, I was following with great interest Doctor Adamkiewicz's work concerning the transferability of anaphylactoid oedema. The main objection then was that this might be the result of a mere transfer of dextran from one animal to another. But, as we have just seen in these consecutive transfer experiments, the problem is not quite that simple. In fact, the evident effect of different glycemic states on anaphylaxis, on immune hemolysis, and on the anaphylactoid inflammation, together with the presence of an antibody in the serum of rats allergic to egg-white, constitute a good justification for a complete re-evaluation of what Doctor Adamkiewicz has called "the physiology of sugars" in regard to hypersensitivity in general.

I think it can be safely predicted that these studies have just provided a way that will undoubtedly stimulate much further investigation to definitely prove "the inadvisability of severing the links between the anaphylactoid and immunologic phenomena." I shall conclude, therefore, by saying that it is quite stimulating to see how such an apparently simple reaction as anaphylactoid oedema could have acquired such extent and scope in the hands of one of us.

B. Halpern: Je vais me permettre de dire un mot, en tant qu'immunologiste. Je suis surpris d'entendre que le Dr. Adamkiewicz emploie le mot "allergène" pour le dextran et le 48-80. Il est impérieux dans toute science, et l'immunologie est une science exacte, d'utiliser les termes conformément à leur définition. Or, le terme "allergène" ou "antigène" a une signification précise. Un antigène est une substance qui provoque une réaction immunologique spécifique, soit sous forme de synthèse d'anticorps, soit sous forme d'hypersensibilité retardée. Or, on n'a jamais démontré la présence d'anticorps ni pour le dextran ni pour la polyvinylpyrrolidone, qui est un autre histaminolibérateur, et encore moins pour le 48-80 qui est une substance syn-

thétique de faible poids moléculaire. Bien qu'on ignore encore le mécanisme par lequel ces substances déterminent une libération de médiateurs chimiques, elles n'agissent certainement pas par un processus immunologique. De ce fait, il ne convient pas de les dénommer "allergènes."

V. W. Adamkiewicz: Monsieur le Professeur Halpern, je crois que les questions de nomenclature posent en effet une difficulté en allergologie. Malheureusement, les mots expriment rarement ce que l'on croit qu'ils expriment avec autant de clarté qu'ils n'en donnent l'impression. L'allergie, c'est surtout une entité clinique caractérisée, du reste assez vaguement, par des critères cliniques. Ce qui la déclenche se nomme un allergène. Donc allergène est un terme générique s'appliquant à tout déclencheur d'allergie. Une des sous-classes d'allergènes, peut-être la plus importante, consiste en des antigènes. Une autre se compose encore toujours de facteurs physiques et chimiques divers tels: le froid, la chaleur, la formaldéhyde, le dextran, etc. L'allergie déclenchée par les allergènes-antigènes découle d'une aberration du mécanisme immun. Celle qui est déclenchée par les allergènes non-antigéniques procède d'un mécanisme en voie d'être élucidé.

Je concevrais, quoique je n'en verrais pas l'utilité immédiate, de faire de l'allergène un synonyme d'antigène. Le sens du mot allergie se restreindrait alors seulement à l'aberration du mécanisme immun déclenché par un allergène qui est un antigène. Par contre, tout ce qui se passerait quand l'allergène ne serait pas un antigène cesserait d'être allergique. Ainsi le dextran ne causerait pas d'allergie chez le rat et deviendrait alors un: allergénoïde, antigénoïde, allergoïdogène, anaphylactoïdogène, etc. Mais de faire du mot allergène un synonyme d'antigène requerrait une redéfinition préalable du mot allergie lui-même.