Intravenous glucose therapy

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INTRAVENOUS GLUCOSE THERAPY

A Consideration of the Physiological Principals, Indications, Concentrations, Dosage, and Rate of Administration.......

UNIVERSITY of NEBRASKA COLLEGE of MEDICINE

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Robert Best
INTRODUCTION

If we wish to discard the more or less mythical and apocryphal references to blood transfusion in ancient literature, the suggestion to introduce blood or medicaments into veins did not formulate itself into man's mind, according to Fantus, until after Harvey, 1613, discovered and demonstrated the circulation of blood.

Macht states that the first actually to inject drugs intravenously into animals belongs to the architect and professor of astronomy, Christopher Wren, who in 1656 injected dogs with drugs by means of a quill attached to a small bladder. After that, intravenous injection was not practiced until about 1900.

In 1907 Fleg made roughly timed intravenous sugar injections. He noted the remarkable diuresis and realized the possible clinical application. Litchfield in 1909 began to use hypotonic glucose solution (15 grams to the liter) intravenously. In 1914 he started using hypertonic solutions in the same manner.

The first clinician to advocate treatment of hepatic diseases with dextrose was A. P. Beddard in 1909. According to Fantus, Erhlick, in 1910, with the introduction of arsenphenamine made intravenous injection a matter of every day practice.

The next pioneer in this type of therapy appears to be Kausch, who in 1911 recommended and attempted intravenous nutrition in hysterical vomiting and hyperemesis gravidarum, surgical conditions and acute gato-intestinal disease.
INTRODUCTION

In 1914 Henriches reported the use of 30% glucose intravenous for the treatment of heart disease. In 1915 Opie and Alford and independently Graham furnished the experimental basis for this therapy by demonstrating that the feeding of carbohydrates lessens the susceptibility of rats and dogs to necrosis of the liver caused by chloroform and by phosphorus.

Bernard Fantus states that intravenous injection was discovered and practiced earlier than hypodermic injections.

The reader will observe that the term glucose is very generally used as synonymous with dextrose and sugar. Until dextrose was accepted by the Pharmacopea it was commonly known by the synonym "glucose" and this latter term is occasionally used even at present time to describe dextrose.
PHYSIOLOGICAL PRINCIPALS

There are certain fundamental facts about carbohydrates that are so well established and so well known as not to need discussion. According to La Fetra, sugars, dextrins and starches are the most economical source of energy. Some being absorbed as ingested and others requiring but little digestive effort. They furnish energy chiefly for heat maintenance and muscular activity. They build up the glycogen reserve and may be converted into stores of fat. They spare proteins thereby lessening the amount of nitrogen excretion otherwise necessary. Moreover, they may be utilized to build up certain useful amino acids. They can replace the fats to a very large extent up to the point of not causing deficiency in the fat soluble A and the anti rachitic vitamins. They serve when properly utilized to prevent acidosis.

Grafe states, that the fate of sugar in the liver varies according to the needs of the entire organism or the momentary demands of the liver. He gives four possibilities: 1. It may be carried off to the peripheral blood stream through the hepatic veins unchanged. 2. It may be synthesized to glycogen. 3. It may be decomposed to CO2 and H2O. 4. It may be converted into fat or protein elements. Glycogen is the form of carbohydrate used for storage. He states it is astonishing that the amount and rate of glycogen formation depends on the quantity of glycogen already deposited in the cells. In starving animals the deposition of glycogen is more difficult than under other circumstances. The glycogen content of the liver
PHYSIOLOGICAL PRINCIPALS

is normally 4 - 5% and cannot be made to exceed 14%. The main duty of sugar is to act as a calory producer. It is particularly well adapted to this role because of the ease with which it is oxidized. Lactic acid is the most important product of decomposition and can be most readily determined. The quantity is small under conditions, but this is because the lactic acid which reaches the blood stream is quickly synthesized by the intact liver into carbohydrate.

It has been shown by Flood, Bodansky and others that dextrose is most rapidly absorbed into the blood stream and existed in the blood stream as such.

Holt investigated healthy children from 1 to 18 years and found that about 51% of the distribution of calories was derived from carbohydrates of which about 1/2 of this was given as sugar. Gebhart found that the healthy active boys of St. Paul's school consumed 600 grams of carbohydrates daily or nearly 2,500 calories daily. Much of this being in the form of sweets. Dun, Phillips, Henske, Best, McCoogan and Wherry state that carbohydrates provide easily utilisable energy and heat. They are stored in small amounts, a normal starving adult using up his available glycogen stores in 36 to 72 hours. The bulk of the average diet is in the form of carbohydrates. Carbohydrates usually furnish 40 to 70% of the total calories of a diet.

Finkelstein has emphasized that though carbohydrate does not itself enter into the composition of cell cytoplasm it induces retention of protein salts and water being the chief influence by which water and water-containing constituents
PHYSIOLOGICAL PRINCIPALS

are stored. When food is given by any route which involves absorption as a prelude to its entering the blood stream the rates which it will enter will depend on the rate at which it is absorbed. By any route of administration but especially by the oral route, the actual rate of entry into the blood stream and hence into the tissues, according to Woodyatt, Sansum and Wilder, must vary with a wide range of physical, physiological and pathological conditions over which we have no control.

Hendon says when a measured quantity of any substance is introduced into the alimentary tract or the subcutaneous tissues the balance between delivery and distribution is preserved by the physiology of digestion and absorption.

Starches administered by the oral route are changed to maltose a disaccharid by the diastatic ferment, ptyaline of the saliva. This in turn is acted on by a ferment and becomes glucose or dextrose. These processes are carried on in the mouth and later in the stomach until acted on by the HCL of the gastric secretion when they are stopped. The amylase of the pancreatic secretion and other less important ferments complete the transformation of the starch to glucose in the intestines. The glucose is rapidly taken up by the portal circulation and transported to the liver whence it is synthesized to glycogen (often spoken of as animal starch). The liver stores the glycogen. The maximum quantity which it may contain varies in different animals, being about 10% by weight in man. The glycogen is given off to the general circulation as glucose. This change occurs at such a rate that normally the percentage of sugar in the
blood remains constant at a level of from .10 to .12 per cent. Some of this glucose in the general circulation is not made use of immediately by the cells but is re-synthesized to glycogen to be stored as it was in the liver. The main subsidiary store house is in the muscles. These can take up glycogen according to Mosenthal, in amount equivalent to .5% to .9% their weight. This is an amount approximately equal to that found in the liver.

Claude Bernard, who discovered glycogen, thought it was a secretion of the liver because he found that it could be produced by this organ on a diet devoid of starches. Later glycogen came to be regarded as a storage produce of carbohydrate material, much in the same manner in which fat is regarded as a storage produce of lipid material. Recently, the work of Barbour, Chaikoff, Macleod and Orr and others undermined this conception by showing, in the first place, that it is impossible to rid the liver entirely of glycogen, which should be the case if it were purely a storage product; and, in the second place, that during starvation the amount of glycogen in the liver at first is markedly diminished but later increases again. These facts were responsible for a new theory of glycogen, namely, that it is an essential step in glyconeogenesis, and that the amount of it in the liver at any given time represents the balance between continuous processes of production and loss.

According to Garnstein and Swarzmann in normal animals, administration of suitable amounts of dextrose leads directly to deposition of glycogen in the liver. In diseases of the
liver, such deposition of glycogen has been denied because the reduction of dextrose tolerance frequently seen in cases of hepatic damage was interpreted as indicating failure on the part of the liver to remove dextrose from the blood for storage. For the correction of this condition, insulin is being commonly advocated, especially abroad.

Macleod states that although the glycogen in the liver may in part at least be regarded as a storage form of surplus carbohydrates much the same as starch is in plants, there is an accumulating evidence to indicate that it has another function. It represents an obligatory stage in the conversion of those portions of the food stuffs that are to be used for combustion purposes in the organism. It has been shown by Best, Hoet and Marks, according to Macleod, that glycogen can be deposited in the muscles out of the sugar carried to them in the blood, provided insulin is present.

Litchfield states that glucose is non toxic, it is quickly utilized by the organisms, it is the best sparer of nitrogen, it is a stimulant to the mechanism of cell metabolism, and it is easily obtained and prepared.

According to the United States Dispensatory, dextrose, which is sometimes improperly called glucose in chemical literature, may be obtained from grape sugar which is the re-crystallization product of the complete hydrolysis or conversion of the starch by acids. It usually occurs in the hydrated form C₆H₁₂O₆·H₂O and is a colorless crystal of a less sweet taste than sucrose. It is very dextrorotary from which fact it takes the name of dextrose. It was introduced into the U. S. P. and the British Pharmacopea in 1914.
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It is generally and logically accepted that nothing can be more basic or fundamental in the supportive treatment of any serious disease than to supply a patient with food and water in such a form and by such a route that they are immediately available to the starved and thirsty tissues. Glucose is the only food, according to Macleod, existing outside the human body in the same form as that found in the blood stream. Most of the sugar in mamillarian blood is glucose. It has been demonstrated by Slemons' simultaneous analyses of maternal and fetal bloods that the nutritive exchange through the placenta is almost entirely in the form of glycogen. In the artificial feeding of infants, according to Potter, the carbohydrates play a most important role. Not only do they supply the necessary calories not furnished by the fat and the protein, but they also are necessary to complete the oxidation of the fats, otherwise ketone acids would be formed and an acid intoxication intervene. In diseases of the liver, insufficient glyco- genesis causes 'internal' carbohydrate starvation, which results in a reduction of hepatic glycogen, probably largely through depletion of that part of it which serves as a storage form of carbohydrate. According to Althausen, there are several ways in which dextrose, and the same applies to glycogen, has been proved to have an allaying action in hepatic injury. In the first place, dextrose neutralizes many exogenous and endogenous toxins. This may be accomplished by partial oxidation to less toxic compounds or by complete oxidation to carbon dioxide and water. Another
path lies through conjugation to nontoxic glycuronates. The latter is known to occur with cresola, phenola, salicylates, camphor, and many substances containing these compounds. And in the second place under carbohydrate therapy, repair of the injured liver proceeds much more rapidly. In the third place, administration of dextrose reduces prolonged coagulation time in jaundice. He also states that it is unfortunate in hepatic disease when the liver is in urgent need of glycogen, its supply of this substance should be low. He thinks the reason for a low level of glycogen in the injured liver is important clinically, and that experimental data suggest that the lowering of hepatic glycogen may be due, not to an inability on the part of the liver to store glycogen, but to abnormally slow production of new glycogen from non-carbohydrate sources—in which case administration of dextrose would be the indicated remedy. To test the ability of the injured liver to store glycogen, experiments were carried out on rabbits. After poisoning with phosphorus, the damaged livers doubled their content of glycogen three hours after a single oral administration of 2.5 grams of dextrose per kilogram of body weight. The absolute increase of hepatic glycogen in these experiments was much smaller than in normal rabbits, but the low initial level of glycogen in the liver of the poisoned animals must be taken into consideration because the same was also observed in normal rabbits, in which the glycogen of the liver was markedly reduced by fasting or by medication with thyroxine. A somewhat different series of observat-
ions was made on a group of patients with marked abdominal operations. These patients received preoperatively various amounts of dextrose orally or by intravenous infusion. A small wedge-shaped piece of the liver was removed in each instance for microscopic examination. It has been shown in animals that the liver loses half of its glycogen after one hour of ether anesthesia—all patients were uniformly fasted over night and operated on in the morning. For a control group, several patients were used from whom biopsies of the liver were obtained prior to 1925, when such cases were still treated surgically without an intravenous infusion of dextrose as part of the preoperative routine. One group of patients received 50 to 100 grams of dextrose by mouth three times a day for from one to two weeks preoperatively. In addition, these patients were given intravenous infusion of dextrose twelve hours before the operation. Another group of patients was given two intravenous infusions of dextrose (from 500 to 1,000 cc. of 10 per cent solution) a day, for from one to five days, the last injection being given on the morning of the operation. In these three groups, biopsy specimens of the liver with approximately equal degrees of damage were compared microscopically in regard to their content of glycogen. The slides were also compared with sections of rabbit liver containing known amounts of this substance. Biopsy specimens from fourteen patients in these three groups were examined in the described manner. From a comparison of typical sections—it is readily seen that the livers of patients who received no dextrose before
operation are almost devoid of glycogen and closely resemble that of the rabbit with a glycogen content of only 1.5 per cent. The parenchymatous cells of the liver in these sections are narrow, and their cytoplasm takes a dark stain. The sinusoids and bile capillaries are wide. On the other hand, the hepatic cells in sections from patients who received large amounts of dextrose by mouth are literally filled with glycogen and have the appearance of those of the rabbit with 10.8 per cent of glycogen in its liver. The cells in the thirs group, in which the patients received dextrose intravenously, contain only moderate amounts of glycogen---The probable reason for this is that patients in this group received considerably less dextrose than those in the second group. The author's observations prove that even the severely injured liver in the rabbit and in man does not lose its ability to store glycogen, but will do so to a marked degree when sufficient exogenous dextrose is provided. This also supports the view that the low level of hepatic glycogen in diseases of the liver is due to a shortage of carbohydrate in the body, caused by slowing of the transformation of noncarbohydrate material into dextrose. When enough sugar is supplied to relieve the persistent demand on the liver for more carbohydrate this organ at once begins to store glycogen. The fact that lipemia, ketosis and relative hypoglycemia are observed in cases of hepatic disease and also in starvation is another link in this chain of evidence that in diseases of the liver there is an internal hunger for carbohydrate.

Administration of dextrose is indicated when it is desired:
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According to Althausen:

1. To reduce the working load of the liver.

2. To correct metabolic derangements due to hepatic insufficiency.

3. To aid detoxication, especially if the toxins are of unknown origin and cannot be otherwise eliminated.

4. To favor rapid regeneration of hepatic parenchyma.

5. To shorten prolonged coagulation time in jaundice.

One or more of these indications are present in all primary diseases of the liver and also in cases of secondary functional hepatic insufficiency. It is desirable to give to patients with hepatic disease rather large amounts of dextrose because, by supplying enough of it for all energy requirements, one is sparing the liver the effort of producing dextrose from noncarbohydrate sources. The human body at rest, according to Althausen, requires 30 calories or, 8 grams of dextrose per kilogram of weight. An individual weighing 70 kilograms needs, thus, 560 grams of dextrose. Assuming that daily about 300 grams of carbohydrate can be readily obtained from the diet, there remains 260 grams of dextrose which can be supplemented advantageously. This figure will be higher if the patient is permitted physical activity. Sections from the liver of patients who received dextrose in amounts satisfying all energy requirements demonstrate by their high content of glycogen that the desired objective had been reached. The best way of giving carbohydrate diet with additional feedings of from 50 to 100 grams of dextrose in fruit juice three times a day. More dextrose can be given with ease by mouth than in any other way. In rectal administration of
dextrose the amount absorbed when it is given in dilute solution is too small or uncertain, whereas concentrated solutions are irritating to the colon.

Recent investigative work by Pressman, Levi, McNealy and Smith, working separately, have shown that little if any dextrose is absorbed by the rectal route.

In further support of the intravenous route in preference to rectal injections McNealy and Williams have shown that dextrose is apparently not absorbed by the colon, though salt solution is taken up more readily. However, Taylor states that glucose can be used as a rectal meal with or without normal saline, and that children derive great benefit from this in addition to ordinary diet. According to Althausen, intravenous instillation of dextrose— is, from the point of view of an increase in hepatic glycogen, equally but not more efficacious than a similar oral dose. On the other hand, deposition of glycogen in the heart and the skeletal muscles is greater with the use of the intravenous route and maybe advantageous in diseases of these organs. However, in diseases of the liver, intravenous administration of dextrose is to be preferred only when emesis or some other cause makes the oral route unavailable.

Polak, Mazzola, Zweibel, Physiologists; tell us that glucose is:

1. A food for the vital organs, especially the liver and heart muscle.

2. That its use temporarily improves the quality of the pulse by improving the ventricular filling of the heart.
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3. That it temporarily raises the systolic blood pressure and produces a peripheral circulation by its osmotic effect on tissue fluids.

4. That it promotes diuresis and combats acidosis.

5. That it temporarily lowers body temperature.

6. That it increases the protective power of the blood; and according to Hofbauer it stimulates the production of myelocytes.

7. That it decreases the coagulation time in jaundice patients but increases the clotting time in other patients.

8. That in high concentration it prevents agglutination of the blood and in diabetics, glucose, and insulin effect glycogen storage of the heart.

They state that three conditions which attend all operations in varying degree are shock, dehydration and acidosis. In the prevention of shock, concentrated glucose solutions by intravenous injection play an important part, this also holds true in its treatment. Out of a study of more than 200 cases of primary shock and shock and hemorrhage, all of which have been given a 50 per cent glucose solution, these authors contend that hypertonic solutions have a therapeutic action on the vital organs of the body by their action on the circulatory system, and by their proper use the patient can be prepared for the strain of an operation and her postoperative safety, comfort, reaction and resistance are increased.

In any well-developed case of traumatic shock with or without hemorrhage there is a partial suspension of the cir-
culation associated with an actual decrease in the volume of circulating blood---The diminished blood volume bears a definite relationship to the severity of the patient's condition, but not to the actual amount of blood lost by hemorrhage, for even after considerable bleeding there is a rapid return to normal of the blood plasma volume and the cell volume. If this occurs (this sensitization to the loss of blood), no untoward symptoms develop. When, however, the blood loss continues or is excessive and there is severe trauma besides, a condition of profound shock follows.

Experiments on animals, according to Polak, Mazzola and Zweibel, that hypertonic solutions of glucose affect the circulation by acting on the heart muscle, temporarily raise the systolic and pulse pressure and improve and diminish the rate of the pulse by restoration of the blood volume. When concentrated glucose is given prior to operation and there is considerable hemorrhage, there is a sharp drop in the systolic pressure with only a gradual fall in the pulse pressure. In contrast similar amounts of blood loss in the controls have been followed by an abrupt fall not only in the systolic but in the pulse pressure as well. After injections of hypertonic glucose, the pulse pressure promptly rises, reaches a maximum in about 30 minutes and after 60 to 90 minutes gradually comes down to the normal. The systolic pressure has a primary fall and gradually increases and remains slightly at a level above normal. The rapidity and duration of its effect is proportionate to the quantity of solution injected, the pulse rate is always diminished.
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The improvement of blood supply by raising the arterial pressure is one of the most important means of treatment of wound shock. He gives two methods: (1) drugs which constrict arterioles and (2) by increasing the volume of blood in the circulation. It is primarily important to get nutrition to the tissues—hence it is obvious that the pressure means nothing unless this is obtained. Baylis has shown that the hemoglobin may be reduced to as low as 25 per cent of the normal. He states there is general agreement that Ringer's solution is useless in raising low blood pressure in wounded men. It has been found that there is a temporary rise followed by a rapid fall to the previous level or to lower levels. Experiments on cats confirm this experience—if part of the blood be removed and immediately replaced by Ringer's solution, the blood pressure is not completely restored to its original height and within one half to one hour it returns to its low level or lower. Glucose solution have sometimes been recommended on the idea that there may be a carbohydrate starvation in wound shock. Cannon found that the blood sugar is above normal in shock. This might be supportive to Altenhausen's belief that due to injury, trauma, etc, the liver for some unexplained reason gives up its glycogen.

Rans and Arlson found that a 5.4 per cent solution of glucose had only a transitory effect in raising blood pressure in rabbits. Baylis concludes from this that there is no object in adding glucose solution for intravenous injections. However, this is unjust from the standpoint that he was using a hypotonic solution in cases where the blood volume was
already below normal. de Caus says shock is caused by sudden hydration of the protein particles and their consequent precipitation in the capillaries and pericapillary lymph vessels which they obstruct. The lowering of the body temperature is due to the absorption of heat by the hydrating particles. In mild forms of shock the blood collects in the big veins. In mild or prolonged shock congestion is selective and confined to one or more of a few of the important viscera. The value of glucose lies in dehydrating rapidly these protein particles.

In an experimental study of the effects of intravenous injections of hypertonic glucose solution (50%) on the circulation of the cat, Mazzola and Torrey, state that shock is due to blood stasis in capillaries, transudation of plasma into tissue spaces, difficult oxygination of tissues and diminished blood supply. It follows that treatment must aim to diminish circulatory stasis. It is agreed that blood is the best fluid to inject. In the absence of this they conclude that 50 per cent glucose will produce a final sustained reduction in pulse rate. Slow injection is preferred. They contend that a preoperative injection of 50 per cent glucose will diminish a fall of blood pressure in a foretold hemorrhage. Maxwell states that nothing relieves post-operative shock, vomiting and acidosis as promptly as glucose.

Bernard Fantus in his book on "The Technic of Medication" states that blood pressure is not raised by hypertonic infusions. Sugar solutions produce however, a dilatation of the
capillaries whereby the venous pressure is raised.

Intravenous sugar has been most effective in controlling the acute vomiting and intoxication of pregnancy. Its value as a supportive measure in any medical or surgical crisis cannot be disputed. Sprague contends that intravenous use of sugar solution appears rational in diseases in which readily available food is urgently needed by active organs like the heart.

(Hayden) Chloroform can destroy one half of the liver tissue in a fasting animal and that with a high carbohydrate diet this liver tissue can be repaired in seven to nine days. Both chloroform and ether cause hyperglycemia followed by lessened glycogen in the liver. Intravenous injection of dextrose and a high carbohydrate diet are indicated before and after anaesthesia in liver disorders. According to Titus glucose injected intravenously as a therapeutic agent in various medical and surgical conditions, has a wide application. The protective action of diets high in carbohydrates is apparently based on an abundance of glycogen in the liver. On the contrary, a low glycogen content of the liver affects unfavorably certain functions of the liver. Diminished tolerance to dextrose follows the reductions of hepatic glycogen.

Von Noorden and Isaac claim that the reduction in tolerance to dextrose of animals with low hepatic glycogen is due to diminished glycogenogenesis, the rate of which depends on the existing supply of glycogen from which energy for polymerization of dextrose is derived through its transformation into lactic
acids. In accord with this theory is the work of Geiger on a hibernating frog, in which marked depletion of hepatic glycogen interferes with the ability of the liver to synthesize lactic acid to glycogen. Another function of the liver, that related metabolism of pigments, also becomes disturbed with a decrease in hepatic glycogen. According to the work of Sang with human beings, increased urobilinuria appears whenever carbohydrates in the diet are decreased below a certain level. Of the greatest importance in deficiency of glycogen in the liver is the impairment of the hepatic function of detoxication. Experimentally, Sansum and Woodyatt found that animals treated with phlorhizin are easier to kill with chloroform than are normal animals; while Davis and Bollman noticed that such hepatic poisons as chloroform, carbon tetrachloride and phosphorus are more effective in animals with a reduced glycogen content of the liver.

Guttmann found that under nutrition markedly increases the incidence of arsphenamine icterus. Baehr and Klemperer observed similarly that diabetic patients on a low carbohydrate diet took arsenical therapy poorly and frequently developed jaundice.

According to Stone, Williams and Ewing working separately on toxemia pregnancy, the liver is always affected showing areas of focal necrosis. They agree that the liver is the glycogen or sugar storing organ and also detoxicating organ of the body, and it functions less powerfully as such if depleted of its sugar, as is proved by the fact that an animal starved of carbohydrates may be killed by a smaller
dose of any poison than is required for a similar animal
that has been well fed. The experiments of Davis and
Whipple also have shown that starved animals are especially
susceptible to liver injury from chloroform and other
poisons, whereas sugar and diets rich in carbohydrates
exert a marked protective action against such liver injury.

The question of the essential nature of hepatic gly-
cogen is of interest to any one attempting to influence the
content of glycogen passed through the three stages and is
now entering a fourth stage.

Titus has shown that in experimentally injured livers
the addition of insulin to dextrose administration has the
effect of reducing the glycogen content of the liver. It
is desirable to give patients with hepatic disease rather
large amounts of dextrose because, by supplying enough of
if for all energy requirements, one is sparing the liver
the effort of producing dextrose from non-carbohydrate
sources.

The supply of a suitable amount of hypertonic glucose
solution intravenously, according to Litchfield has the
following effect. The general appearance improves at once.
The features are less pinched. The patient looks brighter
and less "toxic". The respiration becomes slower. The
pulse amplitude is markedly and persistently increased.
Erlanger noted much more effect from glucose than from con-
trol injections of salt solution. The tongue becomes moist.
The patient asks for water and food. The kidneys and bowels
become active. If the patient was restless or delirious he
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becomes quiet and often goes to sleep while the injection is being given. Sprague has used the injection of 50 cc. of 50 per cent glucose in the treatment for congestive heart failure, diphtheric myocarditis, coronary thrombosis in which shock was the presenting factor and paroxysmal dyspnea.

According to Wood and Ross patients suffering from acute toxemia notably those of infantile dysentery due to Flexner's bacillus, are definitely benefited by small transfusions, in conjunction with the administration of fluids by the intravenous and other routes.

The administration of dextrose has also been shown to be of value in treating the crisis of exophthalmic goiter, the toxemias of pregnancy, eclampsia, postoperative vomiting, recurrent vomiting of children, asthma, epidemic encephalitis and in the preparation of poor surgical risks for operation.

According to Titus, a further result of carbohydrate depletion is the consumption of body protein. This "toxic destruction" of protein is especially marked during the course of febrile diseases. Under such conditions the administration of carbohydrate in assimilable form, such as dextrose, acts to spare the protein of the body from destruction. Dextrose may be given by mouth and is then more rapidly utilized than other forms of carbohydrate as it requires no digestion and is quickly absorbed. When oral administration is not feasible because of food intolerance, or when more immediate effects are desired, recourse may be had to intrain-
venous, intramuscular, subcutaneous or intraperitoneal injection. There are certain conditions associated with carbohydrate depletion and ketosis in which the administration of dextrose has proved especially effective as a therapeutic agent. Recurrent or cyclic vomiting of childhood is associated with derangement of carbohydrate and fat metabolism and often accompanied by dehydration. The administration of carbohydrate is indicated to prevent the accompanying acidosis, but only too often no food or fluid can be retained by the stomach.

The parenteral administration of dextrose solutions provides the necessary carbohydrate in utilisable form and also relieves the dehydration. Dextrose is given in 10 per cent solution intravenously in an amount of from 10 to 20 cc. prt kilogram of body weight. According to Hill and Adelman, the dextrose injections are much more effective if insulin is administered at the same time in an amount not exceeding one unit of insulin to each 3 grams of dextrose.

With subsidence of the vomiting, dextrose may be given by mouth dissolved in fruit juices, or as dextrose candy. In diabetic coma, ketone acids accumulate because insufficient dextrose is being utilized to provide for the perfect metabolism of fats. Dextrose is present in excess but cannot be used because of insufficiency of insulin. There is virtually a starvation in the midst of plenty. Under such circumstances the administration of insulin permits the dextrose present to be metabolized, and if the amount of dextrose is sufficient, the ketone acids present may be
completely transformed. In some cases of diabetic coma, however, the amount of ketone acids present may be so large in proportion to dextrose that complete conversion does not occur, even when sufficient insulin has been administered to provide for the metabolism of the accumulated dextrose. It is in such cases that the administration of extra dextrose has been recommended by Bulger and John Levi and others.

It would appear at first sight illogical to administer dextrose to a diabetic, and although there is some difference of opinion, it is nevertheless possible to administer larger amounts of insulin and to cause a more rapid disappearance of the ketosis when dextrose is administered simultaneously. The intravelous injection of dextrose combined with insulin has a further advantage in relieving dehydration and promoting diuresis and also, according to Levi in restocking the liver and heart muscle with glycogen. Levi further recommends the use of dextrose combined with insulin in preparing diabetics for surgical operations. He advises the administration of 250 cc. of 10 per cent dextrose together with 20 to 25 units of insulin.

For severely athreptic infants Marriott advises the administration of a 10 to 20 per cent solution of dextrose intravenously in amounts up to 25 cc. per kilogram of body weight, repeated at daily or more frequent intervals. The dextrose may be given alone or may be combined with insulin in an amount not exceeding one unit to each 2 grams of dextrose.

In the treatment of post-operative shock with acidosis,
the combination of dextrose and insulin is especially effective. (Fisher, Snell and Wade--Authors) For this purpose a 10 per cent dextrose solution is given slowly intravenously in amounts of from 500 to 1000 cc. and insulin is injected subcutaneously in an amount corresponding to one unit to each 3 grams of dextrose administered.

In the presence of severe desiccation of the body, or anhydremia, a symptomatology closely resembling that of surgical shock is seen. The blood becomes concentrated and diminished in volume. Anhydremia occurs as the result of decreased fluid intake, vomiting, excessive heat or the severe diarrhea of Asiatic Cholera or of cholera infantum or "alimentary intoxication" of infants. When anhydremia occurs, fluid is urgently needed, but often cannot be retained by mouth, so that intravenous, subcutaneous or intraperitoneal administration becomes necessary. Dextrose solutions present certain distinct advantages over normal saline, inasmuch as salt injection may result in a dangerous accumulation of chlorides in the body. (Hartmann and Straus).

Dextrose may be completely utilized, leaving behind only water to restore the normal fluid balance; in addition, it serves to supply necessary nutriment. It has been shown by Tisdale, Drake and Brown that the dextrose tolerance of infants with alimentary intoxication is distinctly increased, and Karelitz working in Shick's clinic, has reported excellent results in the treatment of alimentary intoxication by continuous intravenous infusion of dextrose solution.
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In pneumonia, dextrose appears to be of particular value. As early as 1914 Henriques and Anderson observed good results following the administration of 25 per cent dextrose solution intravenously to pneumonia patients. The injections were given three or four times daily in amounts of 250 cc. at a time. Litchfield used a similar technic. During the influenza epidemic of 1918-19 dextrose was used extensively, usually intravenously in the form of a 10 per cent solution given at frequent intervals. More concentrated solutions, up to 50 per cent have been used with the idea of relieving pulmonary edema according to Koons, and Meyer.

Bennett and Dodds advocated the administration of fairly large amounts (200 to 500 grams daily) of dextrose by mouth to patients with pneumonia. MacLachlan, Kastlin and Lynch gave up to 500 or 600 grams of dextrose a day by mouth, and in the case of severely toxic patients administered additional dextrose in the form of a 25 per cent solution intravenously four to six times daily. In a carefully controlled series of observations by MacLachlan and his associates, the mortality from pneumonia was distinctly less in a group of patients who received generous amounts of dextrose as compared with a control group.

In other bacterial toxemias and septicemias, dextrose appears to be of definite value, especially in those cases in which the administration of food by mouth is impossible or impractical.

In the toxemia or severe diphtheria there occurs a
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disturbance in carbohydrate metabolism associated with a depletion of the glycogen reserves according to Schwentker. This appears to be a factor in causing the associated cardiac failure. The administration of dextrose alone or of dextrose and insulin has been shown to influence favorably the course of diphtheria, especially in those cases associated with cardiac failure. Edmunds and Cooper showed that the administration of a 10 per cent solution intravenously prevented cardiac death in the case of dogs poisoned with diphtheria toxin. Toomey, used injections of 25 per cent dextrose intravenously in amounts of from 50 to 75 cc. at frequent intervals in cases of severe diphtheria with cardiac failure and noted that this led to a decrease in cyanosis, a rise in systolic and diastolic blood pressures and general improvement of the patients. In the treatment of severe toxemia with early circulatory failure in diphtheria, Schwentker and Noell recommend the administration of 20 cc. of a 50 per cent solution of dextrose intravenously repeated in from 12 to 24 hours. Following this a 10 per cent solution in somewhat larger amounts is injected at frequent intervals. In addition insulin in an amount of one unit to each 2 grams of dextrose is injected subcutaneously. Kostyal reports a reduction of mortality from severe diphtheria to about one-fourth in a series of patients treated by intravenous injections of dextrose and insulin.

Severe burns are accompanied by a toxemia and concentration of the blood. The injection of large volumes of 10 per cent dextrose solution intravenously serves to supply fluid
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to dilute the concentrated blood to promote diuresis and to diminish the symptoms of toxemia.

In nephritis, the administration of dextrose solution intravenously is often effective in bringing about diuresis, decreasing edema and relieving uremic symptoms. When dextrose in hypertonic solution is given it draws fluid into the blood from the waterlogged tissues and leads to its excretion by way of the kidneys. Not infrequently there occurs simultaneously a lowering of the high blood pressure accompanying uremic states. Dextrose solutions of a concentration of 10 to 25 per cent may be employed for intravenous injection and should be given slowly. It is usually inadvisable to combine the dextrose with saline, as the salts must be eliminated by the disabled kidneys. The administration of dextrose alone introduces nutriment without throwing any load on the kidneys and often is followed by lowering of the non-protein nitrogen and urea of the blood. The extra supply of available carbohydrate serves also to restore the glycogen reserves of the overstrained heart of uremic patients.

Dextrose has an apparent specific affect in protecting the body, especially the liver, against certain poisons and its administration also favors the elimination of poisons through the diuresis produced. Dextrose is of particular value in preventing the toxic affects of chloroform, ether, alcohol, the heavy metals and hydrocyanic acid, according to Opie and Alford, Graham, Davis and Shipple. Consequently the feeding of carbohydrate and the intravenous admin-
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Administration of dextrose has been recommended preparatory to the giving of anaesthetics and as a measure for relief of post-operative toxemia. Kritschewski demonstrated a protective action of dextrose against the toxicity of arsphenamin. Dextrose has also proved of value in the treatment of poisoning with barbital and its derivatives. Sanderson administered 300 cc. of 20 per cent dextrose intravenously to a patient who had taken 200 grains of barbital and noted rapid recovery from the toxic symptoms. Anton and Jacobi have shown that alterations occur in the carbohydrate metabolism in morphine addicts and in a small series of cases they were able to prevent withdrawal symptoms when fairly large amounts of dextrose were administered by mouth during the period of treatment.

Several reports have appeared on the use of dextrose in the treatment of angina pectoris, according to Meyer. A 20 to 25 per cent solution of dextrose is used and 10 to 25 cc. injected intravenously at a time. This often results in a lowering of blood pressure and an amelioration of the symptoms. The fall in blood pressure is attributed by Weil to a dilatation of the capillaries and by Michels to a change in the colloidal condition of the serum.

Increased intracranial pressure resulting from fractures, cerebral hemorrhage, tumors, meningitis, thrombosis, obstructive hydrocephalus and acute cerebral edema may be lowered by the administration of hypertonic dextrose solutions intravenously. Hayden recommends such use of hypertonic dextrose in the preparation of patients for intra-
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cranial operations and Kennedy and Wartis make use of a 50 per cent solution of dextrose in amounts up to 100 cc. injected intravenously two or three times in the 24 hours for the relief of intracranial pressure. Concentrated salt solution have also been used, but hypertonic dextrose is preferable because of its more prolonged action, non-toxicity and absence of terminal rise in blood pressure. Dextrose is of further value in increasing blood volume, controlling acidosis and in providing food, especially in those patients who are vomiting as the result of the intracranial condition. In epidemic meningitis not infrequently the accompanying edema of the spinal cord results in a blocking of the flow of the cerebrospinal fluid. For the relief of such blocking, Stookey, Elliott, and Teachnor have used a 50 per cent solution of dextrose intravenously and have noted a free flow of spinal fluid following the injection.

SUMMARY

Glucose solution is the only food that can be given by the intravenous route. This method of administration is to be restored to, only when emesis or some other cause makes the oral route inadvisable. It is non-toxic and no harm is done if some spills in to the urine. It is a readily available source of food and water for starved and thirsty tissues. It acts to neutralize endogenous and exogenous toxins. If given in hypertonic concentration it acts as a diuretic.
CONCENTRATION DOSE AND RATE OF INJECTION

There appears to be a considerable range of difference of opinion in regards to what is the proper amount of dextrose to be injected for full therapeutic effect, what is the concentration or percentage of dextrose dilutions to be used and what is the proper rate of injection.

Erlanger and Woodyatt, in their work on shock, and Litchfield in his intravenous use of glucose for pneumonia, according to Titus, were pioneers in developing this therapeutic measure. Woodyatt, Wilder and Sansum have demonstrated by clinical experiments that 0.8 grams of glucose per kilogram of body weight may be given per hour without causing glycosuria. This indicates, therefore that the average dose for a normal person is about 1 gram for each kilogram of body weight. An average woman weighs between 50 and 60 kilograms so that from 50 to 60 grams of glucose is a full dose. More than this may be spilled out through the urine but, because its appearance there is of no particular significance, it was decided to establish the figure of 75 grams as the usual initial dose, subsequent doses to be 50 grams. Those clinicians who give less than a therapeutic dose should remember that this is comparable to administering 1/50 or 1/100 grain of morphine, and expecting the usual effect merely because it is morphine.

Titus and Lightbody in their report of investigations to determine a therapeutic dose of dextrose administered intravenously, state that the most favorable results seem to follow the use of the strongly hypertonic solution. They and their co-workers prefer a 25% solution. They state that the inter-
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change of sugar from blood to tissue is more rapid in the stronger concentrations. The concentrations to be selected must depend upon a desired effect and the condition of the patient. Care being taken not to over tax a weakened heart. They continue, that the proper rate of injection appears to be a fixed matter—not more than 8 grams per kilogram of body weight per hour, as was worked out by Woodyatt, Wilder and Sansum.

According to Titus, the under dose has been the common fault and this with loss from too rapid administration may account for the frequent lack of results. Weak solutions possibly contribute to reactions and certainly overload the circulatory system in too short a period of time if sufficient quantity is given to carry a therapeutic dose of the glucose. It should be dissolved in distilled water instead of salt solution as has been variously recommended, because injections of the latter combination seem so often to be followed by unpleasant or even dangerous reactions.

Althausen accepts the dosage and concentration worked out by Woodyatt, Sansum and Wilder. He adds that this figure will be higher if the patient is permitted physical activity.

According to Horsely, Shelton and Horsely the rate at which the intravenous flow of dextrose and Ringer's solution should be maintained depends entirely on the conditions. In hemorrhage or shock, it should be rapid enough to secure almost a normal blood pressure, if low it is impossible to overload the heart until the blood pressure has approximated what
is normal for that individual. For other conditions than shock or hemorrhage the solution should be given at a rate of from 75 to 200 cc. per hour.

Maxwell gives the average dose for an adult as one gram per kilogram of body weight, and the appearance of sugar in the urine after 50 to 70 grams of dextrose, simply represents the kidney spill and is not of great importance. A 25 per cent solution is a very satisfactory concentration, as its use is followed by more rapid and pronounced effects. The hypertonicity favors a more prompt interchange between the blood stream and tissues and therefore quicker utilization by the body. If larger amounts of water are required, a 10 per cent solution may be used with safety; lower dilutions, however, are inadvisable for many unfavorable results have occurred from the overloading of the vascular system with large amounts of a weak glucose solution.

Lynch and Webster in their intravenous glucose treatment of pneumonia, as soon as the diagnosis was established, gave their patients an intravenous injection of 250 cc. of warm 20 per cent glucose-saline solution. The concentrated solution was chosen with a view to putting the least possible strain on the circulatory system of a patient already cyanosed and congested. This injection was given daily in the mild cases and twice daily in the severe ones. It was continued until 24 hours after the crisis. A gravity system was used entirely, and took at least 15 minutes to administer the 250 cc. of solution.

The clinical experiences of Hendon indicate that the rate of administration has as much to do with the subsequent
results in intravenous therapy as does the substance that is used. He states for the average adult individual this rate is approximately 200 cc. of fluid an hour, or a range of between 4,000 and 5,000 cc. of fluid in the twenty-four hours. The estimate of physiologic tolerance has been based, first, on the fact that patients receiving that amount of fluid at the rate here indicated are free from chills and sudden elevation of temperature, which regularly occur when solutions are suddenly or rapidly introduced directly into the circulation. de Gaux states glucose solution, to exert its full effect, must be used within twenty-four hours of its preparation. He always uses and recommends a 10 per cent solution at a temperature of 100 degrees F. Before an operation it must be given slowly, or it will rapidly be excreted by the kidneys. When it is administered slowly any excess is absorbed by the liver as glycogen and let loose into the blood stream in the form of glucose as required. If the patient's protein particles are already hydrated, the glucose can be given faster than when it is merely desired to increase the glycogen reserves.

Polak, Mazzola, and Zweibel states in traumatic shock where the blood pressure falls to a very low reading, the introduction of a 50 to 100 cc. of a 50 per cent solution of glucose will raise the pressure from 15 to 50 millimeters of mercury within a period of four to five minutes. This rise is maintained from 20 minutes to one-half hour, when there is a slight secondary drop followed by a gradual rise in both the systolic and pulse pressure. These observations
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have been confirmed in the animal as well as by more than 200 studies in the human being.

Weir and Walters in treating pyloric obstruction to relieve dehydration and furnish food do not hesitate to give 10 per cent glucose in 1 per cent saline or water, two or three times per day. In cases of hepatic insufficiency a high intake of carbohydrates and fluids is the chief recommendation. This may be accomplished by taking carbohydrates by mouth in addition to solution of dextrose intravenously in doses of one liter once or twice daily. At times this may be increased to 20 per cent strength, 500 cc. being given at one dose. In renal insufficiency--dextrose in solution 10 percent to 20 percent with or without saline one per cent as a diuretic.

Hendon in giving glucose by the continuous drip method generally uses a 10 per cent solution. He governs the daily aggregate amount to be given by the appearance of sugar in urine. He finds that patients suffering with severe toxemia and high temperature will consume at least twice as much dextrose in twenty-four hours as those with low temperature and not affected with toxemia. For example, in peptic ulcer cases he found that an average of one-half pound of dextrose a day seemed to meet their physiologic needs, while in emesis gravidarum and septic infections, one pound a day was the average requirement. Patients with cancer of the colon could consume as much as 11 pounds in six days without showing sugar in the urine. A patient weighing 150 pounds can easily assimilate two pounds of dextrose a day. His experience
demonstrated that no patient need ever die of dehydration or starvation alone and that not only life but a fair degree of physical prosperity can be sustained over a period of at least sixteen days without alimentary feeding; that veno-clysis renders the physician and patient absolutely independent of the gastro-intestinal canal during a given period.

Althausen states that continuous intravenous infusion of dextrose solutions over a period of several days is a procedure that should not be undertaken lightly, owing to the necessity of dissecting a cubital vein for the cannula and the risk of air emboli. On the other hand, when the condition of the patient warrants it, this method of giving the dextrose has important advantages. One of these is the continuous inflow of dextrose without undue strain on the organs of assimilation. Another advantage is the large amount of carbohydrate that can be administered in this fashion...This method of administration of dextrose, which answers the ideal requirements of therapy for cases of severe acute hepatic damage, such as acute yellow atrophy of the liver, has not been given an adequate clinical trial. However, Hendon mentions two patients with multiple abscesses of the liver who recovered following its use.

Pendleton, in working out methods for preventing the agglutination of blood by glucose solution used portions of fresh prepared glucose solution in distilled water and his own blood. Glucose solutions and blood were measured in the stem of a hemocytometer white cell pipette and emptied into the concave portion of a hollow ground slide. The mixture
was made to the same volume in each test (about 0.016 cc.) Air was blown through the pipette into the drop long enough to mix the materials (2 to 3 seconds). A cover-slip was placed over the drop.

The agglutinating power of the following glucose solutions was tested: 5, 7.5, 10, 15, 20, 30, 40, 50, 80 and 100 per cent. One part of blood was used with four parts of glucose solution. Tests showed that this volumetric ratio (of blood to glucose solution) gives roughly the maximum agglutination with solutions of varied concentrations. Solutions containing 5 to 10 per cent of glucose produced decidedly the most marked gross and microscopic agglutination. Agglutination was progressively decreased with each solution of higher concentration. There was no clumping apparent to the naked eye with the 30 per cent solution, but microscopic agglutination was very definite. The 30 per cent solution showed absolutely no gross clumping. The 40, 50, 80 and 100 per cent solutions caused a very loose microscopic agglutination. Thus approximately isotonic solutions (glucose content of 5 to 10 per cent) produced the most marked agglutination.

The next question is what occurs when a glucose solution is mixed with larger quantities of blood as would take place in the passage of the solution into the general circulation? Successive tests were made with 7.5 per cent glucose solutions using a larger proportion of blood each time. With a ratio of blood to glucose solution of 1 to 9 the corpuscles were too much separated by volume of fluid to form large agglutinated masses. Using a ratio of 1 to 4 clumps slightly less
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than 0.2 mm. in diameter formed. They appeared very com-
 pact under the microscope. Stirring with a teasing needle
dissociated practically all clumps, but agglutination was
still present microscopically. On standing, clumps about
0.1 mm. in diameter reformed. With a mixture of equal
parts of blood and glucose solution the corpuscles showed
absolutely no tendency to adhere to one another, but dur-
ing the first minute crenation was maximum for the series
at this point. With a blood to glucose solution ratio of
9 to 1, there was simply a rouleau formation of seemingly
normal erythrocytes. Thus on increasing the blood content
of a glucose solution in successive steps a cycle occurs
in which there is (1) agglutination, (2) absence of agglu-
tination and the appearance of marked crenation, (3) rouleau
formation of apparently normal corpuscles. The 40 per cent
glucose solution produced a similar cycle but in less dist-
inct steps.

In further tests it was found that a 5 per cent solu-
tion of glucose containing 0.2 per cent sodium chloride or
sodium hydroxide to N/250 strength (0.016 per cent by weight)
would cause no agglutination of blood regardless of the relative
amounts of the blood and glucose solutions mixed together.
One-half this amount of sodium chloride or of sodium hydroxide
was not sufficient to prevent agglutination. So less than
one-tenth as much of the sodium hydroxide (by weight) as of
the sodium chloride was required to prevent agglutination.
Agglutination by a 40 per cent solution was much inhibited
but not prevented by 0.2 per cent sodium chloride and N/250
strength of sodium hydroxide respectively.

Acids increased the agglutination. In each test blood was used with 7.5 per cent glucose solutions in the ratio of 1 to 4. Hydrochloric acid in N/1000 concentration seemed to cause about three times the agglutination which occurred in an unacidified glucose control. The presence of citric acid in N/50 concentration in a glucose solution converted the blood into quite firm clumps about 0.8 mm. in diameter. This was the most marked agglutination obtained in the work on glucose.

A 7.5 per cent glucose solution with N/50 citric acid content was tested with varied proportions of blood. This gave a cycle almost identical to that obtained with unacidified solutions except for the greatly increased agglutination by the acidified solution at its maximum point. It is especially noteworthy that, regardless of acid content no agglutination persisted when equal parts of blood and glucose solution were well mixed. Buffer substances in the blood would naturally here greatly diminish the activity of the acid. Tests showed potassium acid phosphate and potassium dibasic phosphate to be anti-agglutinating agents as would be expected because of their potassium content. The pH of N/15 solutions of these salts is 4.49 and 9.18 respectively. No agglutinating properties remained in 7.5 per cent glucose solutions after adding 1.0 to 1.1 per cent of potassium acid phosphate or 0.1 to 0.2 per cent of potassium dibasic phosphate. Here the dibasic salt was at least five times as effective as the mono-basic salt. An N/50 concentration of citric acid necess-
Dilated the use of 1.1 to 1.2 per cent of sodium chloride or only 0.4 per cent of dibasic potassium phosphate. The buffer agent was much more efficient than sodium chloride in preventing agglutination in an acid medium but in the absence of acids its effect was about the same.

A 5 per cent glucose solution containing 0.1 per cent of oxalic acid (a sufficient amount to prevent clotting) caused a slightly greater agglutination than did the unacidified control. With 0.33 per cent of potassium oxalate in a 5 per cent glucose solution there was no agglutination.

Sucrose and glycerin solutions caused an agglutination of blood similar to that of glucose. Sodium chloride and sodium hydroxide inhibited the agglutination. Citric acid and hydrochloric acid increased agglutination. Magnesium sulphate and ammonium sulphate each prevented agglutination by sucrose solution.

As to a possible relationship between agglutination and 'glucose reactions' it might be pointed out that the solution used by Williams and Swett, which they found to give reactions, were approximately isotonic, a concentration producing marked agglutination by our tests. The rise in acidity through autoclaving increases the tendency to agglutination. The means used by these authors in preventing the reaction (faintly alkaline phosphate buffers) will certainly inhibit agglutination in vitro. Of course, if solution be made from water infected with organisms which Seibert has shown to give distilled water reactions there would be an additional point of controversy in explaining
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solution reactions.

SUMMARY

The body utilizes glucose at the rate of .8 gram per kilo body weight per hour.

The concentration should not be less than 10 per cent and may range up to 50 per cent, depending on the desired effect.

The rate of administration should not exceed 500 cc. per hour.
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