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Physiological basis of glucose therapy

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P H Y S I O L O G I C A L B A S I S O F

G L U C O S E T H E R A P Y

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The Physiological Basis of Glucose Therapy.

In the consideration of any form of therapy it is well to think of the rationale for its use. It is with that thought in mind that this paper has been written. An attempt has been made to connect the physiological effects of glucose on the organism with its use as a therapeutic agent. Such a broad view of a subject involves so many aspects that it is quite evident that one cannot completly cover the whole field in such a paper. Never-the-less I feel justified in approaching this subject in this way, rather than by simply considering its use in some disease such as pneumonia, shock & etc. By gaining some understanding of the underlying principles of its use, it is evident that one can use this form of therapy in not only a more intelligent way but also in a greater variety of conditions.

My interest in this subject was stimulated by a thought that has lingered in my mind for sometime. I have felt that the cure of many of the more serious diseases, depended on the strength and resistance of the body, to enable it to combat the disease, rather than on the effect of some specific drug. It was due to this desire of understanding ways of increasing the resistance of the patient that I became interested in this subject. I find, however, that although volumes have been written on glucose therapy, most of the work has been on an emperical basis without an attempt to explain its rationale. For this reason it has been quite difficult to organize this paper and it has only been by picking bit by bit from a large mass of material that it has been possible to logically

develop this subject as intended.

Whenever possible, the principles that have been brought out have been based on experimental data, and well established physiological knowledge. In many instances however it has been necessary to merely state the beliefs of the various authors whether based on experimental evidence or not. In many cases the use of glucose in various diseases has been mentioned and the degree of its success as reported by the various authors. This was for the purpose of showing the scope of the subject and the unlimited possibilities for further development. It goes without saying that in such a limited discussion, all of the aspects of such a broad subject could not be thoroughly considered, but an attempt has been made to bring out the more important phases.

When one considers the subject of glucose therapy it is at once obvious that you are dealing with a substance that is not simply a drug, but is the form into which the body converts all of the carbohydrates, over half of the protiens and about ten percent of the fats in the process of metabolism, Thus, it is evident that to fully consider glucose therapy it would be necessary to consider the effects of carbohydrate diets on various disease conditions. In the consideration of the history of such a subject it would thus be necessary to go back to the earliest beginnings of the dietary management of diseases. It is obvious that this would be impossible so I shall take as a starting point, the period of the development of the commercial product known as glucose.

This product, which was commonly called corn syrup, was developed and became popular in about 1880. The earliest mention of its

therapeutic use, that I have been able to find in the literature, was in 1885 when Middleton (1) published a paper on "The Glucose Product and Suggestions As To Its Therapeutic value". In this paper he cites numerous cases and a variety of conditions in which he had administered large quantities of glucose orally with very remarkable results in many instances. He explained the rationale of this form of therapy on two bases, namely, that glucose not only rests the digestive tract while giving the patient considerable food, but also has a very benificial effect on the glycogenic function of the liver. It was for the latter reason that he thought glucose had special value in cases where the glycogenic functions of the liver were impaired as in the post malarial anemic conditions and etc. He also used glucose in wasting diseases of children, cadaverous people and whenever starch digestion was impaired. In many cases he believed that the digestion, appetite, weight and general health of the patients were greatly improved. From this early period to the present time one can find numerous references to the use of glucose in similar and a great number of other conditions, but as this form of the administration of glucose covers such a broad field and is so vague, I will dwell more on the history of the intravenous administration of glucose.

The earliest authentic records of any type of intravenous therapy dates back to about 1645 when Christopher Wren (2) proved that numerous drugs could be administered by vein. He experimented with a variety of drugs, in humans as well as in dogs, but due to the fact that he knew nothing of asepsis and was working blindly, he naturally encountered bad results so that intravenous therapy in humans was prohibited by law. This method of administration of drugs was not

revived again until the latter part of the 19th century. I could not find any evidence of the use of intravenous glucose in humans during this century but much animal experimentation was done. For example Butte (3) as early as 1888 experimented with six dogs and by testing the oxygen burned while injecting glucose he believed he had proven that glucose was the principal source for the heat maintenance of the body. Time does not permit an explanation of the details of his technic, but it is quite obvious that his results and thus his conclusions were faulty due to improper technic.

The earliest work that I could find on the use of intravenous glucose in the human, was in 1911 when Kausch (4) wrote his first paper on this subject. He had used intravenous nutrition with glucose in numerous conditions such as, hysterical vomiting in hyperemesis gravidarum, acute gastrointestinal diseases, and various surgical conditions. He reports quite favorable results and advises its use in these conditions. The next noteworthy article was in 1914 when Henreques (5) reported 50 cases in which he had used intravenous glucose with good results. His interest in glucose was aroused by his observation, that it had the power to dehydrate jells. For this reason his early work in this field was in nephritic and cardiac diseases in which he found that glucose could be used to reduce the edema. He also used intravenous glucose in various intoxications and stressed its importance in stimulating nephritic function in oliguria and anuria. In some cases he used as high as 250-300 c.c. of 25% glucose per hour. It is quite evident that these early attempts at intravenous glucose therapy stimulated considerable interest and work. From this date on there was a rapidly increasing amount of literature

on the subject. One fact worth noting is the rapid development of intravenous glucose therapy during the world war, especially in the field of shock, hemorrhage and other emergencies. Woodyatt, Sansum and Wilder were among the earliest of the American physicians to use intravenous glucose to any extent, and they are still contributing to this subject. When one considers the great volume of work that has been done in this field up to the present time, it is very evident that in order to make this consideration at all complete, it is necessary to devise some method of organization.

In order to have some basis for the development of the various aspects of such a broad subject, I have tried to divide the physiology of glucose therapy into the various fields that not only seem to cover most of its more important aspects but are also simple enough to be practical. For these reasons the following classification has been devised and an attempt will be made to list many of the important physiological effects of glucose under one of the following headings: (1) The nutritional aspect of glucose therapy, (2) the detoxifying powers of glucose (3) the physiochemical aspects of glucose therapy, and (4) the biochemical aspects of glucose therapy.

The nutritional aspects of the subject will be considered first because it is the phase that is usually thought of when glucose therapy is mentioned. This was probably the effect that was first to be recognized and formed the basis for its earliest application. Such a deduction is quite evident when we realize that food is absolutly necessary for the manintenance of life. Glucose is a very concentrated and easily assimilable form of food. One can realize the value of glucose as a food when we read that Bollman (6) con-

siders that the oxidation of glucose within the normal organism provides the body with 60-90% of the energy essential to existance. Muscular work is practically dependent on it for the necessary chemical changes in the muscle tissue. He also believes that glandular activities, as well as, body temperature requires energy furnished mostly by the oxidation of glucose and gives some experimental evidences to support his views. Thus, when we see the great importance of this form of nourishment in the normal organism under the normal metabolic rate, we can easily see the great demands for glucose in diseases where there is an elevation of temperature or increased activity. It is a well established fact that an increase in the body temperature causes an increase in the metabolic rate. According to Du Bois (7) this increase varies from plus 20 to plus 50. Hewlett (8) puts the figures at plus 10 to plus 40.

The next important point to consider is how long the reserve glucose or glycogen stores will last under fasting conditions and what takes place in the metabolism when these are depleted. This point is quite clearly explained by various authors, all of whom seem to agree on the fundamental principles of the process. Bollman (6) Du Bois (7) Tablot (9) Henry (10) and many others use these principles to explain the beneficial effect of glucose in the acidosis of starvation. They bring out the fact that the glycogen stores are nearly exhausted in 24 hours and from this time until the fat stores are depleted, the nutrition of the body is maintained mostly by the combustion of lipids. This point is quite conclusively

proven by the change in the ratio of the oxygen intake to the carbon dioxide expelled. It is well recognized however, that the liver is forming some glucose at all times, but it is not able to form it fast enough to maintain enough glucose in the system for the complete combustion of the lipids. This incomplete combustion of the lipids results in the formation of ketone bodies such as acetone, diacetic acid and Beta oxybuteric acid. These products being acid in nature must combine with the alkaline reserve which may be reduced to the point that the carbon dioxide combining power of the blood is markedly reduced and the symptoms of acidosis develop. It is self evident that in such a condition the physiological solution of the whole picture would be in the administration of glucose to burn the ketone bodies and thus allow the blood chemistry to return to normal.

The application of the principle is valuable in a variety of conditions, where the intake of available glucose is far below the minimum requirement of the body. Such a condition could be due, either to a decreased intake or an increased demand by the body. It is evident that in serious febrile conditions such as pneumonia, both factors might operate. The increased temperature would cause a higher metabolic rate and thus a need for an increased amount of food, while at the same time the patient may be unable to consume the necessary quantity because of lack of appetite, digestive disorders, and etc. DuBois (7) believes that the maintanence of the proper amount of glucose in such conditions is life saving because the myocardium is on such a severe strain that its nutrition by glucose is most important. The number of diseases in which the application of this principle is

life saving to the individual is quite unlimited. For example, in many cases of stenosis of the esophagus and other parts of the digestive tract, glucose can be used to prepare the patient for surgery, and etc. The life saving properties of glucose therapy is stressed by Titus, Hoffman and Gevens (11) who explain that in many cases of hyperemesis gravidarum, there is an increased demand for glucose by the developing fetus, placenta, and uterus. At the same time the vomiting prevents the intake of food so a very dangerous condition results. In such cases they believe that glucose is often life saving not only for its nutritional, and antiketogenic properties, but due also to i ts detoxifying properties, a subject that I will consider in detail later.

Another phase of the nutritional aspect of glucose therapy that is quite proper to mention at this point is the protein sparing properties of carbohydrates. Cramer (12) who has done considerable work in this connection maintains that the specific protein sparing action of carbohydrates is due to their property of protecting the proteins from being used by the liver for the formation of glycogen. This property should be considered especially in the chronic wasting diseases because by maintaining the proper glycogen reserves one can often prevent the excess destruction of the body proteins. It would be quite proper at this time to discuss the methods by which the glycogen reserves could be maintained by the use of glucose because in this form carbohydrates can be administered in such a variety of ways. This discussion of the various methods of administration of glucose and their technic will be considered later. The next phase of the subject to be discussed will be the detoxifying powers of glucose. This field of glucose therapy has been

developed to the extent that the detoxifying effect of glucose seems to be nearly as valuable as its nutritive value in some conditions.

As an introduction to this field a few chemical experiments will be cited to show the ability of glucose to combine with toxic substances in definite ways to make them less toxic. For example, the simple experiment of combining the phenol derivitive phenylhydrazine with glucose to form the less toxic glucosozone, as well as, other similar experiments can be found in many standard chemistry texts such as Bodansky page 36. The detoxifying powers of glucose are strongly upheld by Bollman (6) who maintains that many toxic substances such as phenols, cresoles, salicylates and etc. form glycuronates and similar products that are less toxic and can be excreted in this form causing little damage to the organism. He also believes that much toxic material is made less toxic by oxidation to less harmful products or even to carbon dioxide and water by the action of glucose. He gives experimental evidence to prove that large stores of glycogen greatly inhibit the action of toxic substances, expecially chlorform and ether.

Von Schwab (14) who has done extensive study and experimentation on the effect of glucose therapy maintains much the same views. He experiments with a great variety of toxic substances as I will consider later. He does not try to explain the reaction of glucose on the toxins in all cases. In case of prussic acid (HCN), however, he believes that not only glucose but some of its intermediary products act on the acid to detoxify it in the form of a cyanhydrin. There has been considerable work done in this same line by many other men. For example, Morette and Muscolina (15) have tested the neutrol-

izing effect of glucose on HCN by testing the potency of the mixture on an animal after having combined the two in a test tube for 24 hours. They have found that 15 grams of glucose can neutralize one gram of HCN and that by first combining the HCN and glucose, a 10 fold lethal dose could be given an animal without any serious effects. Frost (16) goes one step farther and proves that by merely fortifying the animal with large doses of glucose he could protect the animal against a 4 fold lethal dose of the HCN. He explains this action by the antagonistic action of the di-hydroxyacetone that he believes if formed. This substance can protect the animal against a 9 fold lethal dose of HCN. The practical application of this specific effect can be seen not only in cases of poisoning by HCN which is quite frequent due to its use in mouse and rat poisons, but also in much more common conditions if we are to accept the beliefs of Horvath (17). He states that the occurrence of the CN & CNO groups in the normal individual is evident and thus he believes that the value of glucose consists in part in an anti toxic role toward the CN group.

Although Von Schwab (14) is of the opinion that in many cases the detoxifying powers of glucose are due to direct combination with the toxin as in case of mushroom poisoning, xray and foreign protein reaction, auto intoxication and uremea, never-the-less he believes that in many other forms of intoxication where glucose has also proven to be a valuable detoxifying agent, that the results are probably due to the beneficial effect of glucose on the liver. He also points out the following clinical and experimental studies of numerous other men in this field to collaborate his views on the subject.

For example, he points out that in 1920 Blanks treated

several cases of mushroom poisoning with intravenous glucose and Ringer's solution and reports that the results were magical. Steinbrink and Alexander used much the same methods in similar cases and report very favorable results. Pribram who has been quite an an advocate of this form of therapy has used it in cases of intoxication from foreign protein reactions, uremia, nephritis and acute infections where he claims considerable beneficial effects. The work on x-ray intoxication was done by Mahneri and Jacherl who experimented on cats and found that by administering hypertonic glucose solution to the animals after severe exposures to x-rays, significant favorable results were observed. As stated previously, most of these results just mentioned have been explained on the basis of the direct combination of glucose and the toxins, while in the following cases Von Schwab explains most of the beneficial effect on the ability of the glucids to protect the liver.

The work of Kritechewsky and Antonomow (14) gave evidence that both in vitro and in vivo, glucose weakened the toxic properties of salvarsan in rabbits. This was not only explained on the fortifying effect of glucose on the liver but also on the effect of glucose in stablizing the colloidal system which was disturbed by the salvarsan. The favorable effect of glucose in experimental cases of guanidine poisoning as studied by Bokucz, Franks and Hummel was based mostly on this beneficial effect of glucids on the liver. STulsousky has used this form of therapy in cases of poisoning by mercuric chloride ~~poisoning~~ and reports favorable results. Further evidence supporting this theoretical action of glucose therapy is

furnished by Heinekamp. He has shown that by increasing the liver glycogen the animals can stand increased strychnine doses. Other evidences to support this effect of glucose was obtained by a study of the pathological sections of the livers of those animals that had the protection by glucose and those that did not.

Von Schwab (14) collaborated a great deal of this preceding evidence by extensive experimentation on a variety of laboratory animals such as dogs, rabbits, guinea pigs, pigeons, mice and rats. He used a variety of poisons as well, and his work was so extensive that only a few of the most significant points will be given, together with table I to summarize the results. The technic used was very detailed and exacting. He administered the ether, chloroform and prussic acid by inhalation and the strychnine, arsenic and mercuric chloride orally. He gave the glucose in a variety of ways according to the severity of the condition, type of poison and quantity needed. The results were as follows:

animal	Hydrocyanic acid	ether	chloraform	strychnine	arsenic	mercuric chloride
g. pig	+					
dog	+					
rabbit	+		+	+	−	−
rat	+					
mouse	+	−				
pigeon	+					
cat	+					
chicken				+	+	+
frog				−		

Table I

As a summary he makes the statement that in general, glucose seemed to give marked favorable results but in case of HCN poisoning the results were marvelous. He accounts for some of the failures as being due to the difficulty in regulating the dosages of poison and glucose.

The detoxifying power of glucose has become such an important aspect of this form of therapy that there is an unlimited amount of literature on the subject so that a complete survey of the field would be impossible. Simons (18) Davis (19) De Caux (20) are a few of the English writers who have considered this phase of the subject. They report that it has considerable value in cases of phosphorus and chloroform poisoning as well as for prophylaxis of arsphenamine reactions. They explain this effect on the protective action of glucose on the liver as well as by direct combination of the toxin with glucose products as is the case with phosphorus poisoning.

One of the most practical applications of this detoxifying power of glucose is found in its use in pneumonia. According to the statistics and observations of Mc Clachlan, Kastlin and Lynch (21), glucose finds one of its most favorable applications in toxic cases of pneumonia. They give numerous case reports and statistics to the effect that glucose has a definite detoxifying power and is a valuable form of therapy, although it has limitations. Webster and Lynch (23) try to explain this beneficial effect of glucose in such conditions on the basis of its ability to relieve the myocarditis which has resulted from the bacterial toxins. They give experimental evidence to prove this point by producing severe myocarditis in dogs by repeated ascending injections of diphtheria toxin. When the

animals were in various stages of toxicity they gave glucose, digitalis, caffeine and other drugs and made observations. They came to the conclusion that intravenous glucose could be relied on when all others failed. They make the statement, "In many cases glucose was practically life saving, if we could get the solution into the veins before the heart stopped we were certain to save the life of the dog".

There are any number of articles in the literature by men such as Litchfield, Webster, Koons, Bankenshiff, Glaser and etc., who report the use of glucose in pneumonia with quite uniform favorable results. Most men do not try to explain the action of glucose but base their conclusions on clinical results. It is quite possible that the effect of glucose in this condition is due to a combination of a variety of actions such as; the direct combination of glucose products and the toxins, as brought out by Bollman (6) Von Schwab (14) and others; The beneficial effect of glucose on the myocarditis that may exist; The nutritional and antiketogenic action of glucose, as well as, other possible mechanisms that have not been discussed. There is some possibility that even this next phase of the subject that will be spoken of as "The physiochemical basis of glucose therapy" may play some part in the effect of glucose in pneumonia. The physiochemical basis for the use of glucose therapy is one of the most interesting aspects of this subject because of certain properties of glucose that make it such a valuable substance for the control of osmotic relationships. One of these valuable properties of glucose is its lack of toxic effect making it capable of being injected intravenously in quantities sufficient to control the relative osmotic tension between the vascular system and the tissues, without

resulting in toxic symptoms. The normal concentration of glucose in the blood stream is approximately 0.1%. Thus, it is evident that by the use of a 50% solution, injected within certain limits of time, one can produce a greatly increased osmotic tension.within the blood stream. This would in turn take fluids from the tissues and result in dehydration not only of the tissues themselves but also of the cerebrospinal fluid system and the lymphatic channels.

The application of this form of therapy has proven very valuable in many fields of medicine. One of its most firmly established uses in this respect is in cases of increased cerebraspinal fluid pressure. Weed and Mc Kibler (24) have experimented considerably on this subject and have given some valuable contributions. They have shown quite conclusively by very complete studies, that by the use of hypertonic glucose solutions the spinal fluid pressure increases for a short time and then goes down as much as 30 mm. in some instances with only a slow return to the normal. This slow increase toward the normal is the advantage that glucose has over sodium chloride solutions, because in case of the latter the increase may even rise to above the normal. Spurling (37) has collaborated these views through experiments on dogs with freely flowing cisterna magnae. He finds the slight initial increase of spinal fluid with an almost immediate decrease. Kinsman, Spurling and Jelsma (38) maintain the same views and explain them on the power of glucose to draw the water from the tissues into the blood stream. Hill (25) who has applied this principle to many cases of increased intracranial pressure, is a strong advocate of its use. Peet (26) reports the use of glucose in various types of head injuries and

gives indications for its use, as well as for the use of magnesium sulphate. The use of glucose in reducing the cerebrospinal fluid pressure is only one of the many ways in which this dehydrating principle can be used.

The effectiveness of intravenous glucose in the reduction of edema, both pulmonary and generalized, was one of the earliest effects observed in the development of this subject. This action will be considered more in detail later but at present I will only mention the fact that this therapeutic effect has been applied by Blanks and Von Schwab (14), Weidling (22), Meyer and Latzel (30) and others who that will be mentioned when the effect of glucose on the kidney is considered. Berger and Hageman (27) point out not only its effectiveness in causing the disappearance of edema but also in the removal of various histo-retained substances. This fluid attracting power of glucose has been made use of in various other ways.

The value of glucose solutions in replacing blood volume in cases of hemorrhage and shock are based partly on this effect and partly on the ability of glucose to increase the vaso-tonus, according to the views of Berger and Hageman (27). Erlanger and Woodyatt (28), two of the first men to use glucose for this condition, claim its superiority over sodium chloride solutions and base their opinion on the idea that when glucose is deposited in the tissues its form is changed so that it does not cause an increased osmotic tension in the tissues, while the reverse is true with sodium chloride solutions.

This hydroscopic effect of hypertonic glucose solutions has found useful application on the outside as well as the inside of the body, according to Von Schwab (14). He points out that Krauss has

used strong sugar solutions for cleansing wounds and Müller and Wehenschwack have used it to treat vaginal infections.

The extremly hydroscopic action of strong glucose solutions can be seen in their use in the obliteration of varicose veins. It is quite possible that this effect is so severe that there is actual lysis of the endothelial cells with resultant inflammation, fibrin formation and etc. This is becoming a very common use of glucose and I believe the latest concepts on this field are summarized quite well by Geza De Takats (44).

The last point to be considered under the physiochemical aspect of glucose therapy will be the relation between the colloidal system of the blood and intravenous glucose solutions. This subject is far too intricate to consider in detail so only a few clinical studies will be considered. Von Schwab (14) points out the works of Kruechewsky and Antonomow who are of the opinion that the colloidal state is disturbed in many intoxications as in salvarsan poisoning and that glucose is a most valuable agent for re-establishing the colloidal state. DeCaux (20) lays a most important value on this mechanism and explains his views by a very fanciful theory in which he describes a solar like arrangement of the chemical constituents of the blood. He then explains how this relationship is disturbed in certain ways, resulting in shock, thrombosis, hemorrage and etc. He explains the rationale of glucose in such conditions on its great power to re-establish this colloidal state. Much more could be said under the subject of the physiochemical aspect of glucose therapy but most of it is so closely related to the biochemical action of glucose that it will be considered under this heading.

Under the biochemical phase of glucose therapy I have tried to include the actions of glucose that deal more with the biological effect of glucose on the tissues and not so much with the physical effects as in the former division. The first subject to be considered under this heading will be the biological effect of glucose therapy in conditions of shock. Although this form of therapy has been used in shock for a long time, most of its rationale has been based on the idea that glucose only acted by increasing the fluid constituents of the blood. There are possibly some other explanations for the efficacy of glucose solutions in this condition. One of the most interesting pieces of experimentation on this subject was done by Boresheva and Golberg (29). They were working on the assumption that shock, (especially the anaphylactic type), was due to the effusion of fluids from the blood vessels and that glucose decreased this effusion. To prove this theory they devised a very technical perfusion experiments in which they sensitized guinea pig vessels to spicific antigens, and by testing the rate at which the perfusion would increase when the specific antigen was used both with and without glucose, they were able to show that 5% glucose had the ability to prevent this effusion. This action of glucose is ascribed to the supposition that glucose has the ability to prevent the grade of dispersity of the colloids in the muscle cells, that results from the combination of antigen and antibody within the territory of the cell. This experiment is sited not as proof of the action of glucose in shock, but never the less, there is possibly some practical value in these findings. There are also numerous other explanations for the use of this form of therapy, most of

which are not so complex.

Berger, Hageman, and Keel (27) would lay more stress on two other effects that they find operating. Firstly, the ability of glucose to cause the passage of histo-retained substances into the blood stream and thus a plasma increase and secondly, the property of glucose to cause an increased vaso-tonus. They have not given any evidence or explanation, however, of this latter effect.

Erlanger and Woodyat (28) did some of the earliest work in this field and published their first article in 1917. They experimented with various kinds of solutions in shock and came to the conclusion that glucose was best. They explained this efficacy of glucose over other solutions, such as, sodium chloride on the theory that glucose polymerizes in the tissues when it is deposited in same, and thus does not exert much osmotic tension to counteract the osmatic effect of the intra-vascular glucose. Sodium chloride, on the other hand, will collect in the tissues and so balance the osmotic effect of that in the vessels.

There are numerous other theories on this subject that will not be taken up. The theory by DeCaux (20) is possibly the most fanciful explanation for the effect of glucose on shock. This theory was explained under the physiochemical diversion of this paper but it is proper to add at this time that DeCaux used this explanation to justify the use of intravenous glucose in cerebral, pulmonary, and splanchnic shock.

There are enumerable articles in the literature by such men as Peet (24) Levey and Macheca (31) and may others who advise this form of therapy in shock. Peet advises its use especially where

there is a low blood pressure and a rapid or rising pulse. Levey and Macheca often combine it with insulin and state that it is often life saving, especially in late cases where there is an acetone breath and diacetic acid in the urine. A great deal more could be written on this subject but time makes it necessary to take up the next biochemical aspect of glucose therapy.

The next biochemical aspect of this subject to be considered will be the relation of glucose therapy to the liver. In order to make this discussion more complete it would be proper to consider the physiology of glycogenesis and glycogenolysis as well as the colloidal structure of the cell protoplasm and its relation to the content of glycogen. It is at once evident that a complete discussion of this aspect of the subject would be too large for detailed consideration so the more practical clinical views rather than the intricate pathological and chemical processes will be discussed.

The first condition to be discussed under this heading will be the toxemias of pregnancy. According to the views of McConnell (32) there is often a very severe disturbance in carbohydrate metabolism especially during early pregnancy. This he explains on the basis of excessive demand for glucose by the developing placenta, fetus and uterus, while at the same time there is often a decreased intake of food. If this process goes too far the metabolic mechanisms would not be able to supply the liver with enough glucose to insure an adequate glycogen reserve so hepatic degeneration would probably result. The hepatic degeneration in turn would result in decreased glycogen production so that a vicious circle is established. The more the liver is damaged the less glycogen is produced and the more

the glycogen reserve is depleted the more the liver is damaged. Thus McConnell (32) finds that in the early toxemias when the disturbance is of metabolic origin, the employment of glucose is probably the best single therapeutic agent. He also points out that in the other varieties of toxemias of pregnancy, its value is not so specific but never the less, it has much value for its detoxifying and nutritional properties. Titus, Hoffman and Givens (11) maintain nearly identical views as to the etiology and treatment of toxemias of pregnancy. They go one step farther, however, and by experimental evidence they believe they have proven that the decreased liver function that results from the lack of the glucose stores results in a flooding of the body with toxins. They also point out that in their starvation experiments they have produced pathological changes in the liver lobules that are similar to those of fatal toxemias of pregnancy. Glucose therapy has been used for such conditions by these men for many years and they claim marvelous results in most instances. It is quite possible, however, that all of this explanation is not as simple as it seems because as Cramer (13) has quite well proven, glycogen of the liver is not a reserve store of excess carbohydrate but is a production of the secretion of the liver cells. He also points out that this glycogen production is independent of any supply of preformed carbohydrate in the blood. Whether the whole process of the relation of glucose to the liver function in the toxemias of pregnancy if definitely proven or not is hard to say but there can be little doubt as to the value of glucose therapy in such conditions.

The close relationship between the liver and carbohydrate metabolism is seen very clearly in the work of Mann and Magath (33). They have shown that a hepectomized animal will die quite quickly with a definite glucose deficiency and that the administration of glucose will greatly prolong their lives as well as causing their complete temporary recovery when in a comatose stage. They also show that "Eck's Festula" dogs soon show chronic intoxication on a normal diet but with large amounts of glucose they may gain weight and remain in a good condition for a long time. This latter experiment might suggest not only the detoxifying powers of glucose but also the glucose production of the liver.

Another interesting relation between glucose and the hepatic function is the ability of large glycogen stores to protect the liver against the toxic effect of certain poisons. Opie and Alford (36) who have experimented considerably with this phase of the subject, find that the injury to the hepatic tissue is least per each unit of poison if the animal is on a rich carbohydrate diet and greatest when on a high protein diet. Mann and Willamson (35) go one step farther and show how the intravenous administration of glucose greatly improves the condition of the liver after it has been injured by chloroform. Bollemen (6) reports some closely related work in which severe jaundice has been produced in dogs by the ligation of their bile ducts, and shows how these dogs can be maintained in good condition for several months with very little loss of weight, if they are maintained on a high carbohydrate diet. He also reports well marked although temporary improvement in terminal conditions by the use of intravenous glucose. There are numerous other men who base much of the value of glucose therapy on its hepatic action.

Von Schwab (14) puts forth the idea that many toxins act on the liver and upset its normal function, resulting in a disturbance of the sugar metabolism. To combat this effect glucose acts as a specific remedy. He also maintains that the liver is a site for the building of anti-bodies and thus its support by sufficient glucose is quite necessary. This belief is fairly well substantiated by experimental evidence as brought out by Collins, Goldzichr, and Koster (36). They have shown by sections of the liver before and after the administration of glucose, that definite histological changes in the Kupffer cells result from its administration. Thus they conclude that the therapeutic effects of glucose in infectious conditions can be explained by the activation of the reticulo-endothelial system. There are probably many other ways in which glucose therapy is related to liver function but this will be the last one to be considered. The next phase of glucose therapy to be discussed will be its relationship to the renal function.

Although it is quite probable that glucose therapy is much more closely related to hepatic that to renal function, never the less, there are some interesting relationships in this field as well. Although much of the earliest work done with intravenous glucose was on its diuretic and dehydrating powers in nephritic conditions as reported by Henreques (5) in 1914, not many of the other effects were appreciated till quite lately. Bollman (6) reports some interesting experimental evidence of the relation between the nephritic functions and glucose therapy. He points out that bilaterally nephrectomized animals that receive intravenous glucose, remain in much better condition than those not treated in this way. He also states

that he has seen marked temporary improvement from symptoms of uremia following its use. In most cases the animals have regained consciousness from coma and have stopped having muscular twitchings and convulsions. They have even stood up, walked soon after they were apparently ready to die. Many Much the same favorable results were reported in cases of severe nephrosis and nephritis.

There are numerous other men that maintain similar views. Wiedling (22) advises the use of glucose in nephritis, not only because of its diuretic action but also for its nutritional and detoxifying power. Pribram (14) believes that this detoxifying power is of great value in cases of uremia. Henreques (5) and Fisher (39) who did much of the earliest work in this field, used glucose mainly as a diuretic. They report its favorable effects in cardiac and renal edema, as well as in the anurias and aligurias of various kinds. Bollman (6) points out the work of Tbuka who has found that glucose can be used to stimulate transplanted kidneys to activity when they refuse to function. The diuretic action of glucose is quite well established at present, but much depends on its rate of injection and concentration in order to obtain the desired results. Woodyatt, Wilder, and Sansum (40) were the first to put this diuretic action of glucose on a scientific basis. They have conclusively proven that if over 0.9 grams of glucose per kilogram of body weight per hour is injected there will be an excretion of sugar in the urine with a resulting diuretic effect. In dogs they can produce a diureses of 350-600 c.c. per hour if enough fluid is given. In a 70 kilogram man this would be equal to 19,600 c.c. in 24 hours. This could not be achieved, however, it points out the great diuretic possibilities of glucose.

Although glucose is a comparitively harmless diuretic it is not without some dangers because not only too severe dehydration may result but also the heart may be stopped by vascular conjestion. This could result if very large amounts of concentrated glucose would be given quite rapidly and the patient allowed too much water at the same time. The diuretic action of glucose is evidently a valuable form of therapy but it is also evident that the equipement, knowledge and technic necessary would limit its practical application. This will be the last subject to be discussed under the heading of the biochemical aspect of glucose therapy. There are a few other conditions in which there is a physiological rationale for the use of glucose therapy but they could not be placed under any of the other headings so they will be considered at this time.

The next subject to be discussed will be the fluctuation of the blood sugar during eclampsia, and their relation to the convulsions in that disease. This is a very interesting field but it is of such recent development that the facts are not very well established. The first work in this field was done by Titus and Welketts (41) and Titus and Dodds (66). They have taken blood sugar readings in eclampsia as often as every few minutes and find that there is a sharp drop in the blood sugar just before a convulsion and then an increase during the convulsion so that the reading taken just afterward is slightly above the normal. For this reason they maintain that the convulsion is due to the sharp drop in plasma sugar much as in the case of insulin shock. To explain the mechanism of this phenomenon they state that there is a greater demand for glucose by the system than the metabolism can supply, so there is a decrease in

the plasma glucose. This decrease in plasma glucose in turn makes a readjustment with the cell glycogen necessary. When the cell glycogen is reduced the cells,, even of the nervous system, are made more irritable so the convulsion takes place. For these reasons they believe that the use of glucose in such conditions is based on a scientific rationale rather than on merely an imperical basis. There are other men such as Stander and Harrison (42) who maintain opposite views. They have also taken frequent blood sugar readings and report that they not only fail to find any drop in the blood sugar but that there is often a hyperglycemia. They also find, however, that intravenous glucose is a very valuable form of therapy in such conditions. There is apparently an increasing trend toward the use of glucose in the toxemias of pregnancy but many of the advocates do not try to explain its rationale.

Titus (46) is a very strong advocate for this form of therapy in a variety of toxemias such as hyperemesis gravidarum, acute yellow atrophy of the liver, chorea gravidarum, pre-eclampsia, and eclampsia. There are numerous other men who maintain much the same views, some however, base the application on a purely imperical basis. A few references on this subject will be given but time will not permit further individual consideration. Some of the advocates of glucose therapy in the toxemias of pregnancy are Duncan and Harding (45), Titus and Hoffman (11), Stander and Harrison (42), Lee (43), Weedling (22), and McConnell (32). Some of these articles have been discussed previously in this paper. There has been such a great variety of other diseases that have been rather sucessfully treated by glucose therapy that a full consideration of all of them would be impossible. For the sake of general interest, however, a few of the more important diseases will be mentioned with a word concerning the efficacy

of this treatment.

Although the use of glucose in pneumonia has been considered several times previously under such headings as nutrition, detoxification, myocarditis, and etc, a few references will be quoted concerning the clinical results of this therapy. Litchfield (47), who reported the beneficial effects of glucose in pneumonia as early as 1918, was one of the first men to recognize its value. McClachlin, Kostlin, and Lynch (21) stress its value more in the very toxic cases and advocate very large amounts. Bollman (6) reports very remarkable results with its use in pneumonia in dogs. Lynch and Webster (23) are very strong believers in glucose therapy in pneumonia and say that it is not only a nutritional source of energy but is a valuable detoxicant. By statistics they report its marked superiority over digitalis. Such a great number of men have reported favorable results with glucose in pneumonia that one could quite safely say that it is now a recognized form of therapy for this condition. The use of glucose therapy in a variety of other conditions has been discussed earlier in this paper, but they will be summarized at this time before taking up the new conditions to be discussed.

The following conditions have been considered in their relation to glucose therapy: Hemorrhage, shock, increased intracranial pressure, edema, nephritis, obstructive jaundice, uremia, acidosis, eclampsia, toxemias of pregnancy, pre and post operative conditions, varicose veins, vaginal infections, septicemia, different types of toxemias and poisoning, and even cleansing of open wounds. There

are a great number of other uses that have not been considered previously and will be mentioned at this time.

Von Schwab (14) reports the quite favorable use of glucose in cases of puerperal infection, cardio dystrophy, septicemia, colera, typhoid, dysentary, uremia, alimentary intoxication, meuro retinitis, various infections, as well as poisoning of various types such as mushroom poisoning, roentgen ray intoxication, salvarsan reactions, auto intoxication, guanidine poisoning, mercury, typsin, insulin, strychnine, phosphorus, chloroform, ether and prussic acid poisoning.

Jadassoln and Streit (48) report favorable effects in cases of tetanus and advise that it should be tried more.

Alford (49) (50) has used glucose in 40 cases of epidemic encephalitis and reports marked symptomatic improvement in 34 cases.

McGlasson (51) has used glucose to advantage in various types of dermatitis.

Haden (52) (53) advises the use of glucose and anti-meningoccic serum in meningitis of the epidemic type.

Toomey (54) advises the use of frequent injections ofsmall concentrated doses of glucose for the cardiac and circulatory failure of diphtheria.

Bennett and Dodds (55) mention the somniferous effect of large doses of intravenous glucose.

Meyer and Latzel (30) use small doses of 20% glucose intravenously for intermittent claudication, pulmonary edema and angina pectoris. They report varying success.

Goetsch and Brauder (56) bring out its value in toxemias of various origins such as in burns, hyperthyroid crysis and etc.

Natansen (57) has used intramuscular injections of ten percent glucose solution in myocytis with very favorable results.

Surmant and Tiprez (58) point out the great value of glucose in stenosis of the digestive tract.

There are undoubtedly a great many other conditions in which glucose therapy has been tried but this brief survey will suffice to give an idea of the possibilities for the development and application of this subject. As with many other forms of therapy, however, the fundamental or physiological principles need much development in order to make scientific advance more rapid. Much of the success in glucose therapy depends on the proper method of administration so the rest of the paper will deal with the various ways in which glucose can be given and also with the prevention of reactions.

The oral administration of glucose will be considered first. Although it is quite probable that this was the first route in which glucose was given, it is evident that many men seem to have forgotten its value. Up to the present time there has been very little evidence that the action of glucose is any different whether given by mouth or otherwise. Due to the nature of many conditions the intravenous administration must be used, but except where necessary it is my opinion that the oral route should be used. Due to the fact that glucose is not as sweet as cane sugar and still has the same caloric value, solutions as strong as 20% can be given with some flavoring such as lemon, orange and etc. As high as two or three liters of this can often be given in 24 hours, thus giving not only the increased fluids but also 1,600 to 2,400 calories. Bennett and

Dodds are firm believers in this method of administration because it not only gives the increased calories and fluids without effecting the appetite but it also provides the body with an ideal substance to counteract acidosis. They also state that glucose digestion calls calls forth less motor response and less HCL secretion than most any other food. Although Maclachlan, Kastlin and Lynch (21) are strong advocates of the oral administration of glucose, when ever possible, they believe that in toxic pneumonia cases, they get better results from the same number of calories per vein than by mouth. Another point worth mentioning here is the value of feeding large quantities of glucose or glucose forming foods in early pregnancy, especially in the toxemias. This idea was brought out by McConnell (32) Titus, Hoffman and Gevens (11) Weidling (22) and other men. The merits of the oral administration of glucose is so well established that it will be left at this point and the next method considered

The next route for the administration of glucose to be discussed is its use in proctoclysis. The use of glucose solutions per rectum was such a well established method of administration in the past that it was often a routine post-operative proceedure. There has been much evidence of late that tends to prove that glucose can not be absorbed in this way. McNealy and Wellems (59), (60), have done much scientific experimentation to prove this fact. By taking isolated loops of portions of the large and small intestine and testing the absorption time for glucose solutions they have proven that there is little if any glucose absorbed from the colon. Pressman (16), also gives evidence that this use of glucose is of no value except for the fluids absorbed. He shows that not enough

sugar can be absorbed to even effect the blood sugar of a severe diabetic. He also proves that after 8-24 hours he can recover a great part of the glucose administered and accounts for much of the rest by that used by the bacteria. To further show its uselessness he points out that not enough is ever given in the first place to do much good. 500 c.c. of a 5% solution could only yeald 100 calories if it was all absorbed so it is evident that this method is not very effective.

The next method to consider is the intra peritoneal administration. This finds its most favorable use in pediatrics where the veins are small and vomiting prevents the oral use. Stanford and Hertmeyer (62) advise the frequent use of 100 c.c. of 5% solutions in many cases when it cannot be given otherwise. He states that there are no ill effects so as long as there is no abdominal pathology present and no surgery is to be done. Clark (63), gives some interesting experimental evidence to the effect that 75% of the glucose administered is absorbed in 3 hours but the fluid is slow to absorb in the normal individual. Much work has been done in this line and much has been written on the subject. Most of the comments, however, give no scientific data so it will suffice to say that many men find this method of administration very valuable.

The intramuscular injection of glucose is also an available means for the administration of glucose to children and does not carry the fear of puncturing a viscus. Jeronne and Glasser (64), have used this method a great deal and state that there is very little danger if one knows the contraindications. These are, bacteremia or hyperglucemia. He reports 100 cases with only three tempor-

ary indurated areas. He uses a No. 20 needle and slowly injects a 10% solution into the vastus lateralis and medius until there is the proper tension. The indications for this form of glucose are the same as for any other paraenteral administration and can often be used when other methods are impractical.

One of the most recently developed methods of administration of glucose is by hypodermoclysis. DeTokatts (65) is a strong supporter of this method and says that it is the simplest, most practical and safest way to give glucose. He advocates the use of 5% solutions and states that as high as 2000 c.c. can be given by the subcutaneous drip in 24 hours. This would give a maximum of 400 calories. He describes a rather detailed technic in which he uses a local anaesthesia, small needle, and avoids over distention. He also advises the use of 1,000 c.c. of ringers solution with the glucose solution. The development of this method was stimulated by the too frequent post operative order to give glucose by proctoclysis, a method that is not advisable.

The last paraenteral method of glucose administration to be considered will be the intravenous route. This route possibly lends itself to a greater variety of uses than any other because many concentrations can be used to obtain a variety of osmotic effects, and sufficient glucose can be given to be of real value. Although the various advantages and disadvantages of this method of administration will not be considered now, it is quite necessary to consider the technic of administration. The dosage, concentration and rate of of injection are so very important that some of the high points of same will be considered.

The rate of injection is a very important consideration because it will govern the grams of glucose that enter the vein in a given time and this in turn largely governs its action. For example a strong solution injected rapidly would produce diuresis, dehydration and might cause some cell lysis, while the same solution injected slowly would produce mone of these effects. In the past strong solutions were avoided but the tendency at present seems to be toward the use of about 25% solutions, injected slowly. Titus and Lightbody (66) have studied this problem for sometime and conclude that a 25% solution is advisable in the average case. They agree with Wilder, Woodyatt and Sansum (40), that the maximum rate should not be over 0.8 grams per hour per kilo. In order to work out the proper technic Titus and Lightbody have made graphs of the blood sugar readings while giving the glucose at different rates. They find that after injecting solutions of moderate concentration for over 90-100 minutes there is often an over stimulation of the pancreas causing a drop in the blood sugar that may even lead to a hypoglycemic reaction. According to these findings they advise the use of 75 grams of glucose in a 25% solution, taking 90-100 minutes for injection. They often give 3 or 4 subsequent doses of 60 gm. each in 24 hours to keep up the necessary calories. This is based on the dosage for a 150 lb. man. There are many other men who advise fairly strong solutions. Keeth (67), agrees that stronger solutions are best if time is taken and fluids are properly maintained. Bollman (6) says there are indications for from 10-50% but for the average case 20% gives best results. Titus and Dodds (68), (74), have done much work to prove that 25% is the proper solution. They give the following reasons to support this

view: (1) Less overfilling of the blood stream for weak circulations. (2) Full dose quicker with less fluids for the body to handle (3) Poorly warded- hypertonicity favors more rapid interchange between the tissues and blood stream so the toxins are diluted, edema decreased, and the sugar is seized and stored more rapidly (4) when more fluids are desired 10% can be used, but this is the lowest limit of safty. They maintain that 1 gm. per kilo is the proper first dose and 2/3 of this in subsequent doses. The maximum rate is 3-4 c.c. of a 25% sol. per minute. Matas (69) who has used the continuous intravenous "drip" method with considerable sucess advises 20-30% solutions only for diuretic and dehydrating purposes and in other cases believes as McConnell (70), that 10% is better. McConnell cannulates a vein well above the elbow and uses continuous injection and can give 400 grams of glucose and 4000 c.c. of fluid in 24 hours. Kosaki (71) also uses 10% because he says stronger solutions cause lysis of the R. B. C. Wellems and McNealy (72), advise 5% for the same reason. Horsely (73), on the other hand advises 5% glucose in Ringer's solution. It is the author's opinion that the concentration should be used according to whether one wishes to give fluids, cause dehydration or just give the glucose. In the latter case 20-25% solutions seem to be advisable. It is also quite evident that in cases of severe vomiting, Ringer's solution or sodium chloride should be given as is indicated.

The last phase of glucose therapy to be considered will be the reactions following its intravenous administration. This subject is most important because the fear of reactions might cause one to

fear its use where it is indicated and lack of proper knowledge might lead to bad results at times. There seems to be no single cause for these reactions so a brief review of the various causes will be given. Titus and Dodds (68), (74), who are very good authorities give the following causes: (1) Solutions that are too cold (2) Impure glucose (3) distilled water that is contaminated or contains "Pyrogen", products of dead bacteria (4) solutions that are too old or that have had base added before being sterilized (5) Improper dose, concentration or rate of injection. (6) Improper sterilization with resultant carmalization, sedimentation or contamination (7) last but not least (8) improperly cleaned tubeing. Bollman (6) is in accord with most of this and stresses the use of the solutions before they have had time to culture organisms. Stoddard (75), advises the use of the solution within two hours of the time it is autoclaved at 15 pounds for 20 minutes and also advises the use of a buffer. Ingersol (76), points out much that has been mentioned before and adds that the solution should have a Ph of 6.5 to 6.8. Titus and Lightbody (66), have put forth the idea that over stimulation of the pancreas by improper technic may result in a hypoglycemic reaction. It is the authors opinion that all of these points should be considered if one is to be successful in this form of therapy, because there is considerable evidence to support most of the points mentioned.

Conclusions

1. The rationale of glucose in furnishing a convenient and effective way of supplying nutrition is unquestioned.
2. The value of glucose in counteracting starvation acidosis is substantiated by well established chemical and physiological principles.
3. The detoxifying powers of glucose are well proven by a great amount of clinical and experimental evidence.
4. The value of hypertonic glucose solutions in reducing edema, and cerebrospinal fluid pressure is founded on well established physiochemical laws.
5. There is much physical and chemical evidence to support the use of intravenous glucose in shock and hemorrhage.
6. The use of hypertonic glucose solutions to obliterate varicose veins has a definite rationale.
7. The value of glucose in protecting the liver against injury from certain toxins has been well established by considerable experimental and clinical evidence.
8. There is a well established rationale for the use of glucose in the treatment and prevention of certain types of toxemias of pregnancy.
9. The diuretic action of hypertonic glucose is based on well established principles.
10. The rationale for the use of glucose in eclampsia, pneumonia, myocarditis, and numerous other conditions, is firmly established.
11. Much of the success in glucose therapy depends on the method and technic of administration.

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