have been classed as rachitic, in which a section showed the thickening to be on the convexity of the curve. Possibly, as Dr. Lovett has mentioned here, they may have been syphilitic bones instead of rachitic.

DR. ROBERT W. LOVETT, Boston: I do not agree with Dr. Rugh's mechanics in this matter. We are considering the question of weight bearing strains and I should suppose that the line of weight would be on the concave side and not on the convex side of the curved tibia.

DR. H. R. ALLEN, Indianapolis: You refer to an operation, in which you have the strap arrangement on the outside.

DR. LOVETT: In regard to Dr. Meisenbach's question, I believe we are operating too early in a good many cases of rickets. I personally do not think any patient should be operated on until the lower epiphysis of the tibia, taking that as a standard, has become rounded with a clear outline. As long as it looks indistinct I think it ought to be left alone. At least, that is my experience. When we do operate too early the bone is likely to bleed profusely and cuts like cheese. As a by-product of this investigation I have come definitely to the conclusion that those cases which Dr. Meisenbach mentions are the ones that make the trouble, and that we ought to study our cases with the Roentgen ray and not operate until the subacute stage of rickets is over and the deposit of bone has begun again, because when they are in the subacute stage bones are very poorly provided with lime and are very soft. I thought that we should have a perfectly clear epiphysis before doing an osteotomy or osteoclasis. The difficult point in the whole investigation is in the confusion with syphilis, and it is going to take hard work and exhaustive study to clear that up. I believe the changes of rickets are definite in character and can be diagnosticated in the presence of syphilis, but even the best syphilographers do not know what becomes of the so-called osteochondritis seen in early life.

PROLONGED AND ACCURATELY TIMED INTRAVENOUS INJECTIONS OF SUGAR

A PRELIMINARY REPORT *

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The study of sugar tolerance and the effects of prolonged uniform injections of glucose by vein, of which this is an abbreviated report, was undertaken primarily for the purpose of perfecting an accurate clinical method for estimating the sugar-using powers of different individuals. It was also anticipated that the data which would be obtained could not fail to have other applications, and that the method employed might be in itself of general interest as a means of studying problems of absorption, metabolism and elimination, and have therapeutic application. Expectations concerning all of these things have been fulfilled.

The study was based on certain prior ideas which were in part original and in part conceptions which had been expressed before by Doyon and DuFort in 1901, and by Blumenthal in 1906. These may be stated briefly:

1. It is at present a common clinical practice to estimate sugar tolerance as the number of grams of glucose which can be given by mouth all at once and just fail to cause glucosuria, and having done so to draw inferences as to the power of the individual to *utilize* glucose. But reflection will show that "tolerance" properly conceived as a measure of the power of the body to utilize glucose must depend on the rate at which the tissues are able to abstract glucose from the blood by their combined powers to burn it, to reduce it into fat or to polymerize it into glycogen. It must be clear that this sum of three chemical velocities cannot be expressed in grams, nor yet in grams of glucose per kilogram of body weight, but that the element of time must be taken into account. *Tolerance must be regarded as a velocity, not as a weight. It must be measured and expressed in grams of glucose per kilogram of body weight per hour of time* or in other convenient units of weight and time.

2. When sugars are administered by the stomach, the length of time during which they are actually brought to the cells must depend on the motor power of the stomach and of the bowel and on the rates at which the sugars can be absorbed; and even when they are given subcutaneously or by any other route which involves absorption as a prelude to their entering the blood, the rates at which they enter the blood will depend on the rates at which they are absorbed. By any of these, but especially by the oral method, the actual rate of entry of sugar into the blood and tissues at large must vary with a wide range of physical, physiologic and pathologic conditions over which we have no control; nor will it ever be possible by such methods to force sugar to enter the blood any faster than it can be absorbed. The rate of sugar absorption is a self-limited thing, for when a certain concentration of sugar is once present in the blood, no quantity given by mouth or subcutaneously or intraperitoneally can raise it higher. In fact, if the concentration of blood sugar is raised above a certain point by intravenous injections, sugar passes out into spaces from which it would ordinarily be picked up, the absorption rate from these spaces then being expressible only as a minus value.

3. *The nearest possible approach to a scientifically accurate method of sugar tolerance measurement must consist in direct intravascular administrations,* since only by this method is the variable factor of absorption rates reduced to a minimum. When sugar is introduced directly into the circulating blood, each tissue receives its share in proportion to its vascularity, and absorption plays no part except as it may be concerned in the transfer of sugar from the local capillary to the perivascular lymph, and the taking up by each individual cell of the sugar with which it is bathed.

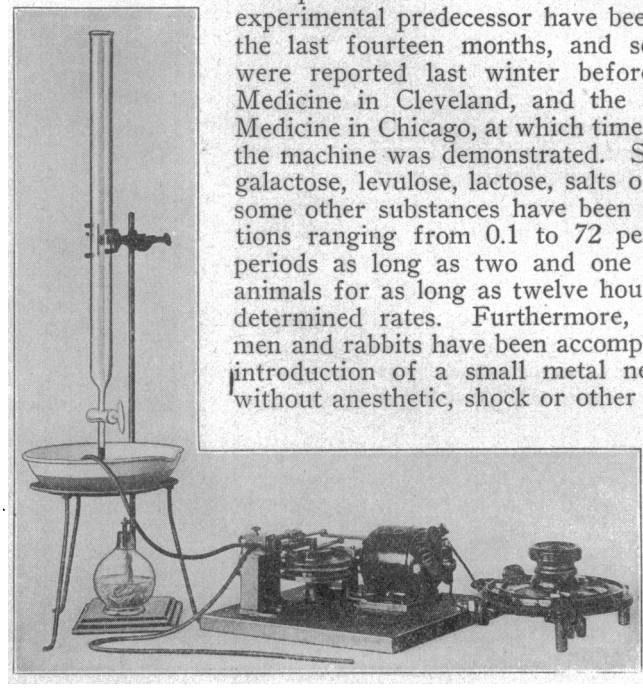
4. When glucose is introduced directly into a vein, we should expect different results with different rates of administration. These different effects might be visualized by conceiving the body as made up of clear transparent tissues with blood like water, while the sugar injection is conceived as an injection of some red dye. If the injection is uniform, continuous and not too rapid, we should first see the dye diffuse through the circulating blood, making the veins and arteries stand out in a deeply colored tracery in the otherwise transparent body. Then the color would begin to "run" from the neighborhood of the capillaries, and, diffusing into the cells, would tint them — at first delicately and in some parts more than others as a histologic section absorbs the stain, then deeper and deeper until the whole mass of tissues were

* From the Otho S. A. Sprague Memorial Institute Laboratory for Clinical Research, Rush Medical College.

diffusely colored. *This would take an appreciable time.* Now if the injection is stopped, the color will gradually fade away as the sugar or dye is used up in the cells. If the injection is begun again, the staining process will be repeated, and so on, the tissues alternately flushing and paling. But if the injection rate is just equal to the rate of utilization, a uniform tint will be maintained indefinitely. If the injection rate is faster than the rate of utilization, the color of the tissues will continue to deepen until they can stain no more, and finally the kidney, sharing in the general picture, drips the excessive stain, and, continuing to do so, the combined rates of excretion and utilization again just equal the rate of injection and the body again maintains steadily a certain depth of color, now of course deeper than before.

It becomes apparent that to determine the utilization rate of glucose in the body, the problem is to find the greatest rate at which glucose can be injected into a vein steadily without causing any glucosuria; and following the foregoing analogy it is clear that the injection must be continued long enough to permit the sugar to diffuse uniformly into the tissues and bring each to its corresponding state of saturation before any conclusion is drawn as to what the final and permanent effects of a certain rate of injection really are. It must also be apparent that a single syringeful of sugar solution injected all at once into a vein represents simply a very high rate of injection for a very brief period of time, and that such a method is the least capable of giving accurate information concerning utilization rates and the general behavior of intravenously administered sugar of any which could be devised. Yet the literature is confused by many fallacious ideas which have been developed out of such methods.

With these principles in mind, we have devised machines for the purpose of giving uniform intravascular administrations at precisely controlled and predetermined rates and for long periods of time.



Apparatus for intravascular administrations. On the right is the quantitative intravenous pump with rheostat for motor speed control; the solution is drawn from a buret which may be more slender than that shown, and fitted with a side neck leading to a second buret of large capacity to facilitate refilling. The rate of injection is checked at intervals by readings on the buret, and corrected if necessary by touching the rheostat. The flame and bath on the left warm the solution. The delivery tube lies in front.

DESCRIPTION OF APPARATUS

The machine consists of a glass syringe barrel with a metal piston provided with a piston ring (record syringe), the barrel being fixed while the piston is actuated by a piston rod from an eccentric on a power shaft. The latter is driven by an electric motor through a worm and gear which reduces the speed of the motor and increases the power correspondingly. On the nozzle of the syringe there is a two way all metal valve of special design which is turned automatically by a cam shaft and alternately permits an influx and outflow of fluid to or from the pump barrel. The rate at which the machine delivers fluid is controlled in three ways: first by the size of the barrel, which is interchangeable so that any capacity can be used from 0.5 to 10 c.c.; second, by a device which regulates the stroke of the piston to any desired length from a millimeter up, and, third, by a rheostat with which the motor speed can be controlled delicately while running so that the pump makes any desired number of strokes per minute between 15 and 60.

The machine is intentionally provided with a surplus of power. It is heavily built and of a high grade of workmanship. It pumps precisely and relentlessly anything from water to an 80 per cent. glucose syrup, at any rate from 10 c.c. to 5 liters hourly, overcoming with negligible variations in speed any minor obstructions which may occur in the tubing or the intravenous cannula or needle. All parts which come in contact with the fluid to be injected are detachable and sterilizable. A photograph of the machine is here reproduced.

Experiments with machines of this type and an experimental predecessor have been conducted during the last fourteen months, and some of the results were reported last winter before the Academy of Medicine in Cleveland, and the Society of Internal Medicine in Chicago, at which times an earlier model of the machine was demonstrated. Solutions of glucose, galactose, levulose, lactose, salts of various kinds and some other substances have been given in concentrations ranging from 0.1 to 72 per cent. to men for periods as long as two and one half hours, and to animals for as long as twelve hours, at precisely predetermined rates. Furthermore, the experiments in men and rabbits have been accomplished by the simple introduction of a small metal needle into the vein without anesthetic, shock or other nonphysiologic factor. For dogs we have employed a small blunt needle provided with a flange, or a very small cannula which was introduced into the saphenous vein under novocain.

The results so far obtained have led us to believe that timed intravenous injections of solutions of known concentration over long periods of time offer a most valuable method of studying a wide range of problems of absorption, kidney function and intermediate metabolism. They also promise to extend the possibilities of intravenous injections for diagnostic and therapeutic purposes beyond anything which has been accomplished heretofore. Some of the principal results may be mentioned briefly in this place.

EXPERIMENTAL RESULTS

1. A normal rabbit, dog or man can utilize between 0.8 and 0.9 gram of d-glucose per kilogram of body weight and hour of time without glucosuria for an indefinite time; that is, d-glucose in 10 to 50 per cent. solution can be introduced directly into the veins at rates corresponding closely to 0.85 gram of glucose per kilogram of body weight and hour of time for from six to twelve hours and not produce any glucosuria. Such rates of glucose administration do not cause any effect which can be interpreted as diuresis.

These facts force certain conclusions, some of which may be mentioned.

(*a*) A man weighing 70 kg., when resting quietly in bed, may receive and utilize 63 gm. of glucose by vein per hour without glucosuria. (This is an accomplished fact). He then receives 4 times 63, or 252 calories per hour, a rate corresponding to 6,048 calories per day. If his resting requirement were 3,000 calories per day, he could thus receive double what he needed, or enough to cover the caloric expenditure of the same man during heavy physical exertion. *Intravenous nutrition with glucose is thus proved to be a feasible clinical proposition,* and the way is opened for experiments with amino-acids, polypeptids, etc.

(*b*) The normal tolerance limit for glucose, expressed as a velocity, is established at close to 0.85 gm. glucose per kilogram of body weight hourly, which agrees approximately with what Blumenthal has established by repeated small intravenous injections in animals.

(*c*) The idea, already in part discredited by the work of Pavey and Godden and others, that the "glycogenic function of the liver" is indispensable for the utilization of glucose, or that it is in any sense necessary as a *barrier* to prevent sugar absorbed from the bowel from being lost in the urine, is definitely laid at rest.

(*d*) The idea that any large quantity of glucose given by vein always causes glucosuria and diuresis is an error based on clumsy methods of study.

2. The intravenous tolerance limit in cases of exophthalmic goiter has been found as low as 0.65 gm. per kilogram and hour, but two cases of acromegaly had a tolerance of 0.85 gm. per kilogram and hour, which is not above the normal, although by the oral method it had not been possible to cause glucosuria with glucose.

3. The tolerance limit for levulose when given by peripheral vein has been found close to 0.15 gm. per kilogram and hour, or only one-sixth that of glucose. For galactose it is even less or about 0.1 gm. per kilogram and hour. For lactose it approaches 0, as known before.

4. When glucose is given by vein faster than at the rate of 0.9 gm. per kilogram and hour, glucosuria appears; then usually a little later, diuresis. When the rate of injection exceeds the normal utilization rate, the time which elapses before glucosuria appears varies. If the injection rate is much too fast, the elapsed time is correspondingly short, or if the tissues have previously been partly saturated with sugar, the same applies. If the injection rate exceeds the utilization rate by about 0.1 gm. per kilogram and hour and the tissues happen to have been low in sugar, it may require several minutes of injection before glucosuria begins. But if a given rate of glucose injection causes glucosuria at all, it always begins to do so within the first half hour. The same general principles apply to other sugars with lower rates of injection.

5. As the rates of glucose injection are increased above 0.85 gm. per kilogram and hour, the rates of overflow in the urine increase also according to definite mathematical laws. At any given rate, say for example 1.8 gm. per kilogram and hour, the glucosuria begins slowly, increases in a steep curve, and finally becomes constant at some level characteristic for this rate of injection. The height of this level, of course, is higher in the case of the more rapid injections and lower for the slower ones. Also the time which elapses before the level is established is the greater the higher the level to be attained. It frequently takes from three to four hours for a glucosuria due to a uniform glucose injection by vein to reach its constant level.

As already stated, about 0.85 gm. glucose per kilogram and hour may be given indefinitely without glucosuria. If we give twice this quantity in the same time, that is, 1.7 gm. glucose per kilogram and hour, there is glucosuria which, when constancy is attained, averages about 0.17 gm. per kilogram and hour. This confirms the older view of Carl von Voit, proved to hold for sugar by Lusk, and Fisher and Wishart, that increasing the concentration of the food in the tissues increases the rate of utilization. But if glucose is given at a rate faster than 2 gm. per kilogram and hour, a large percentage of all glucose in excess of the 2 gm. per kilogram and hour appears in the urine, once constant conditions have been secured.

In a normal individual, the greatest rate of glucosuria which can be produced by feeding any quantity of glucose by mouth is limited, and at most approximates that which is produced by an intravenous injection at the rate of 1.8 gm. per kilogram per hour. Hence it would be reasonable to believe that when sugar is given by mouth in health, it is never absorbed faster than at this rate. This method of estimating an absorption rate by finding a rate of direct intravenous injection which just produces the same effect is, so far as we know, new, and it should be applicable to other problems.

6. As glucose is given at rates exceeding 0.85 gm. per kilogram and hour, and unburned glucose begins to accumulate in the tissues and pass out chiefly in the urine, it carries with it water. With rates of injection only slightly exceeding 0.9 gm. per kilogram and hour, the amount of sugar which escapes burning is moderate, and so the rate of glucosuria and the rate of diuresis are correspondingly moderate. But when sugar is given at the rate of 5.4 gm. per kilogram and hour (that is, 54 gm. hourly for a 10-kg. dog), this is equivalent to giving about 3.6 gm. per kilogram and hour over and above what can be burned. It is like giving 3.6 gm. per kilogram and hour to a total diabetic.

The effect is an incredibly great diuresis. When glucose is given at this rate to a 10-kg. dog, the urinary output rises rapidly to the vicinity of 350 c.c. per hour. If each hour the dog receives enough water to make good the losses, the rate of diuresis or a higher one can be maintained for long periods of time. A 10-kg. dog actually passed in eight hours 2,800 c.c. of urine. This would correspond to 19,600 c.c. for a man weighing 70 kg. in the same time, or an hourly rate of 2,450 c.c. If enough water is not given to counterbalance the urinary water losses, the volume of urine falls and the dog suffers from thirst. Death may be caused in this way. Unless plenty of water is given, not all of the unused sugar can leave the body, since it appears that the concentration of glucose in the urine will not rise above 12.5 per cent. To make 12.5 gm. of glucose pass out of the body through the kidneys, at least 100 c.c. of water are necessary. On the other hand, if one gives too much water with the hourly glucose injection rate of 5.4 gm. per kilogram and hour, there is danger of stopping the heart mechanically. We have produced a diuresis as high as 600 c.c. per 10 kg. of body weight for one hour, and still greater rates

are possible; but attempts to continue such enormous water traffics lead to heart failure. This rate would correspond to an output of 4,200 c.c. of urine hourly from a man weighing 70 kg., or 100 liters in twenty-four hours. *In giving intravenous injections of glucose there are then two things to avoid: too great dehydration on the one hand, and heart failure from imposing too much mechanical work on the other. These can both be avoided by knowing the number of grams of glucose which enter the body hourly, and what volume of water is moved by such a rate of sugar injection.*

CLINICAL APPLICATION

It is hardly necessary to emphasize the therapeutic possibilities which these experiments suggest. With a knowledge of the proper concentration of the solution to be used, and the rate appropriate for this particular solution, we may (1) abstract any quantity of water from the body which we deem safe or desirable, or we may (2) pass through the body a great flushing stream to wash out poisons. How far the principles worked out for normal individuals will apply in disease we have only begun to learn. In this connection it may be well to recall that the literature already contains observations on the use of sugars in therapeutics.

Sugars have been given by mouth or bowel for purposes of nutrition or to obtain other desired metabolic or chemical effects in a wide range of clinical conditions. But as pointed out, such methods of administration do not introduce sugar into the blood faster than an approximate rate of 1.8 gm. per kilogram and hour at most, which is not sufficient to permit much glucose to escape utilization. Hence, after such administrations, unburned sugar does not accumulate in the tissues except to a limited extent, and they are not diuretic except in cases with decreased rates of sugar utilization (diabetes). Intravenous injections may exceed this rate, and so cause, in addition to the ordinary chemical effects of glucose, new physicochemical effects due to the presence of unburned sugar molecules in the tissues, and expressed outwardly as diuresis. Now glucose and levulose have long been found useful when given in cases of diabetic coma, especially when given intravenously. In such cases either mode of administration produces great diuresis, but especially levulous by vein (for levulose the *normal* intravenous tolerance limit being only 0.15 gm. per kilogram and hour). It has not yet been recognized that the value of this treatment is due to the diuresis, but we have on other occasions given the reasons which make us believe that this is the case. In 1907, Fleig[1] made roughly timed intravenous sugar injections, was struck by the remarkable diuresis, and realized possible clinical applications, without making any, however. Kausch,[2] in 1911, recommended and attempted intravenous nutrition with glucose in hysterical vomiting hyperemesis gravidarum, surgical conditions and acute gastro-intestinal disease, but laid no emphasis on the diuretic action. Fischer[3] recommended intravenous glucose injections in conditions of edema, nephritis and intoxication, but especially oligurias and anurias of various sorts on the basis of his observations concerning the power of sugars to dehydrate colloid gels and on their parallel diuretic effects in rabbits and men, thus bringing the behavior of sugars in these respects into relationship with that of diuretic salt solutions and recognizing the physicochemical principles which underlie the beneficial effects of intravenous injections of sugar. In 1914, Henriques[4] reported the use of from 250 to 300 c.c. of 30 per cent. glucose solution in the hour to about fifty clinical cases of heart disease, intoxication, and severe infections, finding special indications in oligurias of nephritis and heart disease. He did not discuss the principles involved. This year Turrettini[5] has given details of three cases of acute nephritis and three of mercuric chlorid poisoning, in all of which the urinary output was favorably affected. Experiments have been in progress in this laboratory for some time to determine the limits of application of these principles and the present technic of administration to different grades of experimental poisoning with mercuric chlorid, arsenic and diphtheria toxin. The system is being tested in the clinic as opportunities offer. Its chief application would appear to be in acute intoxications of various sorts, acute oligurias and anurias, intoxication of pregnancy, and in cardiac and other edemas. Further work is in progress on other diuretics besides sugars and on other sugars besides glucose, and also with simultaneous injections of sugars and salts, such as acetates and bicarbonates.

1. Fleig: Compt. rend. Soc. de biol., 1907, lxiii, 190.
2. Kausch: Deutsch. med. Wchnschr., 1911, xxxvii, 8.
3. Fischer, M. H.: Edema and Nephritis, New York, John Wiley & Sons, 1915.
4. Henriques, E.: Presse méd., 1914, xxii, 121.
5. Turrettini: Rev. méd. de la Suisse romande, 1915, xxxv, 204.

SIGNIFICANCE AND PREVENTION OF AMEBIC INFECTIONS IN THE MOUTHS OF CHILDREN *

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From time to time during more than half a century, a protozoan genus called *Ameba* by some, and *Endameba* or *Entameba* by others, has been reported as occurring chiefly about the gum margins in the oral cavity of human beings.

Few details of the morphology, comparative incidence and pathogenicity of the members of this genus have been given. Until last year, most, if not all of the species, were thought to be nonpathogenic. Indeed, of so little worth were they considered that no mention of their presence is made in the general histologic review of parasitic amebas of man by several authors, who used the term "parasitic amebas" as synonymous with "intestinal amebas."

Thus Craig says:

> There is no experimental evidence connecting *Ent. buccalis* (or the mouth ameba) with disease. It is very doubtful if it has anything to do with caries of the teeth, although it is most frequently encountered in the cavities of carious teeth. However, it may be frequently demonstrated in material scraped from the roots of perfectly normal teeth, so that, as far as the evidence goes, we must regard *Ent. buccalis* as only a secondary invader. The amebae known as *Ent. gingivalis*, Gross, 1849, and *Ent. dentalis*, Grassi, 1879, are probably identical with *Ent. buccalis* and do not merit separate description.

* From the Bureau of Laboratories, Department of Health, New York City.

* Read before the Section on Preventive Medicine and Public Health at the Sixty-Sixth Annual Session of the American Medical Association, San Francisco, June, 1915.