rotation of this loop takes place as it is withdrawn from the umbilical sac at the end of the second month of foetal life. My friend Professor J. E. S. Frazer has made a very thorough study of the mechanism¹ which brings about the turning over of the colic end of the loop. From his observations there can be no doubt, I think, that the retraction of the loop from the umbilicus and its rotation are produced by certain growth bands—or rather retraction bands—which develop along certain sectors of the mesentery of the loop. The rotation of the ileo-colic intestinal loop is a growth phenomenon not unlike in nature to that which we see manifested in the descent of the testicle.

It would take us too far afield in this lecture to discuss the modifications undergone by the liver and stomach with the evolution of the orthograde posture. I shall content myself, so far as the liver is concerned, by drawing attention to the fact that the change in posture was attended, as in the adjacent right lung, by the disappearance of the large caudate lobe. In the human liver a vestige of the caudate lobe is always present, showing that man has come of an ancestry which was pronograde in posture. As for the stomach, I shall merely mention that in the human child this organ is shaped as in anthropoid apes, and occupies the same high horizontal position. At what period of adolescence the infantile form is replaced by the elongated, vertically placed stomach of adult life has yet to be ascertained, but the change in shape must certainly be attributed to man's erect posture.

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- ¹ See Allbutt and Rolleston's *System of Medicine*, Visceroptosis, 1900, vol. iii, p. 860, vol. iv, p. 3. ² H. Tyrrell Gray, *Lancet*, 1920, i, p. 1345. ³ Keith, *Lancet*, 1903, i, p. 632; 1904, i, p. 558. ⁴ *Journ. of Anatomy*, 1916, vol. 50, p. 75.

A NOTE ON THE NATURE OF THE SUGAR IN BLOOD.

BY

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THE recent important advances made by Irvine and his co-workers as to the constitution of the carbohydrates lend themselves admirably to speculation regarding the possible function and significance of the now definitely established "γ" sugars in the metabolic processes of both plant and animal.

Direct evidence of the formation of these reactive isomerides in biological reactions was lacking until the present author and Pryde (Hewitt and Pryde, 1920) showed with some certainty that γ glucose and γ fructose are formed and can be detected when the stable α and β isomerides are in contact with living intact intestine. We contented ourselves with recording the experimental facts, and refrained from discussing any theoretical extension of the work, attractive and obvious as such discussion was, beyond saying, "The possibility thus suggests itself that in the rapid transformation of carbohydrate in living tissues γ sugars may play an important if not an essential part." Later Hewitt and de Souza (1921) remarked with similar reserve on this question, "It may be presumed on *a priori* grounds that a structural change of the nature referred to has some fundamental reason."

Since the communications mentioned above, three publications have appeared in which Hewitt and Pryde's results are quoted in some detail, and in each case are accepted, extended, and employed for the formulation of a theory as to the causation of diabetes mellitus.

Before discussing the evidence adduced in these researches, on which this theory is based, it is perhaps advisable to emphasize the extreme difficulty that exists in interpreting results in this field of work. Most, if not all, of the biochemical data are and must necessarily be indirect; considerable caution is required, therefore, both in devising experiments and in deducing conclusions therefrom if advance is to be made and erroneous conception avoided.

As the known reactions and properties of γ sugars must furnish the final grounds of appeal in discussing their formation or existence in metabolic processes, it might be well to summarize the relevant salient features of such sugars as deduced from the study of their methylated derivatives.

1. They contain an ethylene or propylene oxide ring in place of the butylene ring ascribed to and accepted for the crystalline α and β hexoses.

2. Two γ isomerides exist in the case of each hexose, analogous in their mutual relations to the α and β modifications. Possibly these γ isomers undergo mutarotation *inter se* as well as stereochemical change to the stable form; the last reaction is undoubtedly extremely rapid.

3. The chemical reactivity of γ sugars is very great, and condensation with alcohols to form glucosides takes place rapidly at room temperature. Fehling's solution is reduced in the cold, they unite readily with oxygen to form oxy-compounds, which in turn easily undergo disaccharide formation.

4. Unsubstituted γ sugars show marked instability to traces of acid or alkali.

Such properties manifestly render detection a matter of difficulty, which is further increased when it is remembered that one isomeride of γ glucose is strongly laevo-rotatory, while β glucose is only feebly dextro-rotatory. Apart from isolation of derivatives of these sugars, identification in biological reactions depends on polarimetric determination of optical behaviour and on the reduction of alkaline potassium permanganate.

Polarimetric evidence alone, therefore, must exclude rigorously the presence of β glucose in amount greater than that found normally in aqueous glucose solution in equilibrium. This is referred to in further detail below. The dangers attending the use of permanganate with biological material are obvious; the employment of this reagent requires careful control, and at best can be applied only with extreme caution to such complex solutions as blood or urine.

In my opinion the evidence on which Cooper and Walker (1922) and Winter and Smith (1922) base their theory is insufficient when the essential properties of γ sugars are considered. Cooper and Walker separated blood from a hexose solution (glucose or fructose) by a dialysing membrane and examined, with negative results, the sugar polarimetrically and with permanganate. Several objections can be raised to this technique:

(a) The blood was extravascular and, having undergone at least preliminary stages towards coagulation, was not normal. If it were citrated or oxalated (this is not stated) its condition is possibly still more abnormal.

(b) Owing to physical properties no enzyme could pass from the blood inside the dialyser to the sugar outside. Before any action could take place the hexose substrate would have to pass through the membrane. Unless preferential dialysis of one of the α or β isomerides had occurred no change in the specific rotation would be found, if the sugars were in equilibrium at the beginning of the experiment.*

(c) As the concentration of hexose outside the dialyser was greater than within, no transference of sugar from within outwards would be produced. The value, therefore, of examining the sugar outside does not seem apparent.

(d) Inherent dangers in the use of potassium permanganate exist; as, however, no reduction took place, the inference is perhaps not without reason that no dialysis of any component had occurred in either direction, for the various extractives of blood are far from inactive as regards this reagent, and owing to relative concentration would be removed from the blood inside to the solution which was tested.

Negative results obtained from experiments based on such technique do not warrant the superstructure of theory erected thereon. Hewitt and de Souza (*loc. cit.*) had previously clearly demonstrated what Cooper and Walker attempted.

Winter and Smith (1922), in a more elaborate study, reached the conclusion that the normal blood sugar is γ glucose, and that an enzyme exists (not in the blood) for effecting the transformation of the stable butylene oxide glucoses into γ glucose.

I agree that no such enzyme can be demonstrated in the blood (see Hewitt and de Souza, *loc. cit.*), but am of opinion that objections may be raised both to Winter and Smith's view of blood sugar and to the experimental evidence on which they found their theory.

Dealing with the technique employed by these authors it is to be observed that in the course of preparing their final filtrate for polarimetric examination the following manipulative operations, among others, were performed: (1) precipitation with tungstic acid; (2) heating to 40° C.; (3) addition of ethyl and propyl alcohol and contact with these alcohols for twenty minutes at moderate temperature; (4) concentration

* Possibility of preferential dialysis was apparently not considered. It may be stated, however, that alteration of optical values due to such cause cannot be detected. (Unpublished experiments.)

almost to dryness; and (5) solution in water for at least three days.

Consideration of the known reactions of γ glucose renders it unlikely that such a labile substance would remain unaffected by tungstic acid. Since no strict proof is available as to the action of this reagent on γ sugars this point perhaps should not be stressed. The second operation, heating to 40°C ., is one which undoubtedly hastens the mutarotation of any system of isomeric sugars not in equilibrium. The third operation, treatment with alcohol, appears to be one which would rule out all possibility of obtaining the free reactive sugar. I need only refer to the extraordinary capacity which these sugars possess for undergoing glucoside formation with alcohols, or for condensation with acetone. Finally, the acidity of the filtrate is in itself no small objection to the conclusions reached.

It is thus seen that the technique adopted by Winter and Smith is in its essentials one calculated to remove effectively any γ glucose which may have been originally present, and it is difficult to see how the optical observations of the filtrate throw any light on the condition of the original blood sugar.

Dealing next with the times taken to attain a constant optical value, it may be noted that final equilibrium was not reached till after two to four days. It need only be pointed out that such a slow reaction is not a feature of γ sugars or of their mutarotating derivatives. It is regrettable that more complete data are not given, as it is impossible to analyse as fully as might be desired the optical behaviour of the dilute filtrate with a view to interpreting the nature or course of the reaction. It does not appear, however, that the authors have excluded the presence (or formation) of β glucose, with specific rotation $+19^{\circ}$, in amount greater than that in aqueous glucose solution in equilibrium. Similarly with diabetic blood where the optical change is a downward mutarotation, the possibility of the presence of excess of α glucose (specific rotation $+110^{\circ}$) must be admitted. So far as can be judged, the optical variations observed do not lie outside values arising from temporary disturbance of the equilibrium between the α and β butylene oxide glucoses.

No mention is made of precautions to ensure sterility of the sugar solution kept for four days. Non-sterility of the final material obtained—containing, presumably, substances susceptible to bacterial action in addition to glucose—might well account for optical changes. The action on permanganate of the filtrate, fresh and after standing for several days, is similarly not conclusive. Relatively simple oxidative changes, or even saturation of unsaturated compounds, might account for the phenomena observed. This apparently was not controlled. Winter and Smith (1923) state also "the sugar" (of normal blood—that is, γ glucose) "gives an osazone with the same crystalline form and melting point as that of glucosazone." In this connexion Irvine, Fyfe, and Hogg (1915) have shown that γ glucose "reacts with phenylhydrazine and acetic acid, but is thereby resinified, and, in addition, a definite anilide, or other crystalline derivative, could not be obtained." This observation hardly supports the presence of γ glucose in the blood examined by Winter and Smith.

The experiments of Winter and Smith cannot be regarded as crucial, and the question demands rigorous investigation before the existence of γ glucose in more than normal traces can be accepted as the circulating sugar of blood.

In addition it may be pointed out that Winter and Smith's suggestion as to the non-formation of γ glucose in the diabetic does not in any way account for the downward change in optical values found in blood in this pathological state. If their conclusions were sound the optical value of diabetic blood should not vary on standing under aseptic conditions as there could be no transformation from one isomeride to another and the relation of the optical value to the copper value should be a constant throughout. Evidence from pathological conditions also fails to support the main thesis.

The experimental evidence brought by these authors is not, however, such as lends itself to profitable discussion, but among the many possible complicating factors may be indicated the opposed rotations of the conjugated glycuronates and of the free acid.

While admitting, in the absence of any proof, that the reactive forms of sugars are in all probability of fundamental metabolic importance, it is perhaps not necessary to assume that the normal blood sugar is this modification. If the reserve carbohydrate of plants and animals be considered, in no case (except inulin) is it found that γ sugars are present

in combination and are liberated on hydrolysis. Starch, glycogen, and cellulose are condensation products of stable butylene oxide glucose. (Irvine, 1922; Irvine and Macdonald, 1922; Irvine, Denham, and Hirst, 1922.)

Inulin is exceptional, and shares with cellulose the distinction of being of but small value to man as a source of carbohydrate. Sucrose appears to be the only foodstuff in which a γ sugar is available as such for absorption, and it will be noted that it has to undergo hydrolysis before the γ fructose is liberated. No form of reserve carbohydrate as such behaves as a γ sugar.

The sugar of blood cannot but be regarded as a store of carbohydrate ready for consumption at short notice, and following the analogy of the known condition of other reserve carbohydrates one would not be surprised to find the simple monosaccharide to be the stable butylene oxide modification. Furthermore, if one considers the extraordinary chemical reactivity of γ sugars it is but reasonable to suppose that they would not be in this condition in blood.

It may well be that only when required for oxidative processes would the stable form undergo stereochemical change into the reactive modification, and free γ glucose might have but a transient existence, and might almost be regarded as an intermediate product in the katabolism of glucose. Evidence of this will possibly be by no means easy to obtain. In this connexion also it may be noted that Dakin (1922), after reviewing the literature on carbohydrate metabolism, concludes: "Active glucose metabolism only seems to occur in the presence of living and surviving cells."

Until evidence is brought that γ glucose does exist as the sugar of blood and does not exist in diabetic blood, no theory of diabetes can be formulated as to the relation of these sugars to this pathological condition. Observations are in progress on the optical behaviour of equilibrated solutions of sugars in the intestine of the diabetic organism. It is hoped in this way to obtain a decision on this point.

Summary.

1. No evidence exists that γ glucose is a component of normal blood.
2. Theories of diabetes mellitus demanding the presence of γ glucose in normal blood are without experimental foundation.
3. Formation of γ glucose in carbohydrate metabolism may take place as and when required and the active modification may possibly have no more than a transitory existence.

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ON SEPTICAEMIC INFECTION FOLLOWING OPERATIONS FOR APPENDICITIS.

A PROPHYLACTIC SERUM.

BY

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I HAVE drawn attention in previous communications¹ to a train of symptoms which sometimes follows operations for appendicitis in children, if performed from the third to the sixth day from the commencement of the attack, and always leads to a fatal termination within about forty-eight hours; and I gave reasons for my belief that these symptoms indicated a septic infection of the blood taking place at the time of operation.

In the more recent paper I described a case of this kind, in which a bacteriological examination of the blood was made, and the *Streptococcus faecalis* was found in pure culture. Since that date I have seen four similar cases, in each of which the blood was examined during life; in three the *S. faecalis* was found to be present, and in one *Bacillus coli*. I have not found these organisms in the blood in cases in which these symptoms had not made their appearance.