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.

REFERENCES.

- Cooper and Walker (1922): *Biochem. Journ.*, 15, 455-459.
Dakin (1922): *Oxidations and Reductions in the Animal Body*, Longmans, Green and Co., London.
Hewitt and Fryde (1920): *Biochem. Journ.*, 14, 395-405.
Hewitt and de Souza (1921): *Ibid.*, 15, 657-671.
Irvine (1922): *Brit. Assoc. Reports*, Pres. Address to Sect. B.
Irvine and Macdonald (1922): *Brit. Assoc. Reports*.
Irvine, Denham, and Hirst (1922): *Brit. Assoc. Reports*.
Irvine, Fyfe, and Hogg (1915): *Journ. Chem. Soc.*, 107, 524-541.
Winter and Smith (1922): *Journ. Physiol.*, 1, 57, 100-112.
Winter and Smith (1923): *BRITISH MEDICAL JOURNAL*, i, 12-13.

ON SEPTICAEMIC INFECTION FOLLOWING OPERATIONS FOR APPENDICITIS.

A PROPHYLACTIC SERUM.

BY

HERBERT H. BROWN, O.B.E., M.D., F.R.C.S.,
CONSULTING SURGEON TO THE EAST SUFFOLK HOSPITAL, IPSWICH.

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.

Symptoms of Septicaemic Infection.

The train of events is as follows: The operation is performed on a child on the third, fourth, or fifth day. In some cases nothing but drainage of an abscess is undertaken with as little disturbance as possible; in others the appendix is removed; but in all the infection has already spread beyond the appendix, causing inflammation of the surrounding tissues or actual pus formation.

For the first thirty-six hours, or perhaps a little longer, the child seems to be doing well and all the symptoms are satisfactory. The temperature is often normal, pulse slower than before the operation, abdomen flat, no pain or vomiting. The child usually sleeps well for the first night, and everything appears to be satisfactory. Then a rapid and almost sudden change for the worse takes place; the face becomes pale, the pulse rate commences to rise, the temperature is usually subnormal, the child becomes restless and irritable (this is a very marked feature), then drowsiness with restless intervals supervenes, and an occasional shrill "meningeal" cry is uttered which is very characteristic; in fact, all the symptoms are of a cerebral type—the pupils become dilated; coma with a rapidly rising temperature is followed by death, generally within thirty-six hours of the onset of the symptoms. The clinical picture is a very tragic and striking one, and in each case which I have seen in my own practice or that of others the symptoms have been practically identical.

Post mortem nothing is found to account for death. There is no peritonitis, nothing abnormal in the site of operation, no sign of meningitis.

When my attention was first drawn to these cases, about thirteen years ago, I gave what I believed to be the true explanation of them, and further experience has strongly confirmed that belief. It is well known that patients suffering from appendicitis, even after perforation and abscess formation has taken place, may recover without surgical interference: this was more often seen in former years before operations were as commonly undertaken as they are at present and the disease was spoken of as typhlitis or perityphlitis: the abscess perforated into a neighbouring viscus, generally the caecum, and the patient recovered. Operations, which were performed as a rule later than they are now, some time during the second week, when a large abscess was evident, were attended by little if any danger.

If the infection is very acute or the patient's natural resistance low, Nature unaided by the surgeon is defeated. The appendix wall sloughs and perforates into the general peritoneal cavity, causing a rapidly fatal peritonitis and toxæmia. Nature has had no time to mobilize her forces. But in other cases where the resistance is stronger or the virulence of infection less, and the poison is for a longer period confined to the appendix, toxins leaking through its wall set up inflammatory changes in the surrounding tissues, omentum, bowel, or parietal peritoneum. Before actual pus has been formed, a wall of plastic lymph has been thrown up, covering the surrounding inflamed tissues and shutting off the general cavity of the peritoneum, and at the same time sealing up the lymphatics and blood vessels in the inflamed tissues. It acts like the porcelain of a filter, allowing toxins to percolate through into the lymphatics and blood vessels but holding back the infective organisms—*B. coli* and streptococci. This is the first line of defence.

Its production gives time for the development of the second line, which I believe to be of very great importance—that is, the production of antibodies in the blood. The toxins soaking through the wall of lymph into the blood lead to the production of antibodies, which by the middle of the second week have produced a considerable degree of immunity. There is often at this time (if the patient has been allowed to reach this stage) a considerable improvement in the general condition—the temperature may fall to normal and the pulse rate diminish. The abscess, which is frequently a large one, may be opened without any danger, without even infecting the wound, which has been freely irrigated with stinking pus.

When an operation is performed during the middle of the first week the wall of lymph may be disturbed, or rubbed off, or may not have been properly formed, and a direct inoculation of infective material, containing *B. coli* or *S. faecalis*, into the blood stream may take place. This, after a short incubation period (twenty-four to thirty-six hours, or a little longer), is followed by the onset of symptoms due to septicaemic infection. If the operation is deferred to the second week the blood will have been rendered immune to this infection—the second line of defence will have had time to be mobilized, and these septicaemic symptoms do not appear.

If a case of appendicitis is seen early enough—during the first twenty-four hours—there is no question as to the proper treatment. The appendix should be removed at once. The

post-operative risk is practically nil, and no drainage is required. But if the case first comes to the surgeon at a later stage the right line of treatment is not so obvious, if the dangerous period from the third to the sixth day of disease is present. It might be wiser to wait for several days until the abscess has reached a fair size and the blood has become relatively immune to infection before operating. But there are dangers and disadvantages in delay. The abscess might burst into the general peritoneal cavity. The child is in pain and distress, the parents are anxious and expecting immediate relief by the surgeon. Should the case end fatally after all, the surgeon will be blamed for his procrastination. It is difficult, even if he so wishes, for the surgeon to withhold his hand.

It occurred to me that it might be possible by injecting a prophylactic serum before and at the time of operation and shortly afterwards, to produce an immunity for the time which would prevent or largely minimize the danger of blood infection at the operation if performed during the dangerous period. I explained my views to Dr. Ledingham of the Lister Institute, who discussed the matter with Dr. MacConkey, the bacteriologist in charge of the serum department. Dr. MacConkey very kindly arranged to immunize a horse with cultures of *S. faecalis* and *B. coli* provided from cases of mine, and last March sent me a supply of serum. Unfortunately I have not been able to test the value of the serum as a prophylactic sufficiently, and as in the meantime I have retired from active work on the hospital staff my opportunities have been lessened. But the serum is still available, and I hope, with the aid of surgical colleagues, to be able to give it a full trial, and publish a further report.

REFERENCES.

¹ BRITISH MEDICAL JOURNAL, 1910, ii, 103; *Lancet*, January 15th, 1921.

Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

HYPEREMESIS GRAVIDARUM.

THE following case presents certain features which appear worthy of record:

The patient, a young Jewish lady, had had three pregnancies terminated artificially on account of intractable hyperemesis. She was most anxious to have a child. She became pregnant towards the end of December, 1921, and vomiting began within a few days. She came under my care on January 3rd, 1922. Vomiting was persistent and salivation profuse. I began the line of treatment elaborated by Professor Harding of Toronto. I also administered peptone intramuscularly, having known a number of cases successfully treated by this method by a former partner; in one of these cases the uterus had been emptied twice on account of hyperemesis.

My patient was able to take no nourishment by the mouth except lactose. She improved steadily until on January 16th there was no vomiting and she partook of lemonade, bread-and-butter, and lettuce. Fruit and fish were soon added to the dietary. The condition remained satisfactory until February 14th, when bile was vomited and salivation became profuse. The bilious vomiting increased in frequency and amount, and on February 17th I called in a colleague who had attended her in two previous pregnancies. He expressed great astonishment at her excellent general condition. The bilious vomiting continued with slight intermissions. On March 6th the nurse reported that there had been a slight vaginal discharge. This was brown in colour and odourless. The patient became somewhat restless, but the pulse rate was only slightly raised (90). On the following morning the condition was not improved and the pulse rate had risen to 110. I arranged a consultation with my colleague at the earliest possible moment. When we saw her the pulse rate was 130, and it was decided to empty the uterus, the patient, who was fully conscious, protesting vigorously. The operation was carried out under ether anaesthesia with all possible speed, continuous saline being administered. The heart failed rapidly, and death ensued some hours later.

There were no foetal products recognizable in the uterine contents. Albumin was at no time present in the urine, nor was aceto-acetic acid, but bile appeared in the last few days.

NORMAN WILSON, M.A., M.D., B.Ch.Cantab.

Port Elizabeth, South Africa.