3. That the suprapubic operation should be reserved for stones of very large size or inconvenient shape in boys or girls, or cases of calculus embedded in a sacculi of the bladder or impacted in the mouth of a ureter.

That these propositions are not absolute must be evident. Cases have occurred to myself and others where the lithotrite cannot be introduced owing to some puckering of the mucous membrane of the urethra, and the lateral operation may be forbidden on account of a narrowed and rickety pelvis, but I think it is proved by the above tables that the tendency of surgeons is, when possible, to use the lithotrite instead of the knife, and that with proper care such a course is followed by the best results, and is free from the after-consequences of a cutting operation. At the same time, it is not every surgeon who has had experience of the use of a lithotrite, and to such must be left the choice of one of the other operations. In girls, unless the stone be very large, when it should be removed by the suprapubic operation, lithotrity is always easily available, and it avoids the troublesome after-consequences of over dilatation of the urethra or the danger of a vesico-vaginal fistula.

The advice here given is entirely from the point of view of the patient, but to the practitioner who is called upon to deal with a stone, and who has not had personal experiences of lithotrity, it is difficult to offer suggestions. To see lithotrity performed by Sir Henry Thompson, or some of those who have had large experiences in India, is like witnessing the feats of Roberts with a billiard cue. But the manipulative dexterity which is certainly essential is only acquired by a long apprenticeship and considerable experience. On the other hand the pitfalls of the lateral operation are many and often alarming to those who are not in the habit of witnessing or performing it. The suprapubic operation is in itself simple and easy of performance, and is probably that which under such circumstances should be adopted. At the same time, though I do not place much reliance upon statistics, it is the one that in the above tables presents the most unfavourable results, and in my own, and in the opinion of many other surgeons, the results would appear still worse if it were possible to collect all the cases in which this operation has been performed in recent years.

It must not be forgotten that where there is a stone in the bladder there is or has probably been some amount of pyelitis, and Southam, in his relation of the two cases mentioned above, gives some very good advice with regard to the previous treatment of the patient: Rest in bed, milk diet, and sterilisation of the urine by boric acid or salol given internally, and, if the urine contain much pus, the bladder should be washed out thoroughly more than once with an antiseptic solution. Shock should be avoided by thorough protection of the patient against surface chilling.

There must always be met with some rare cases for which the suprapubic operation is alone available, such as are indicated in the third of the above propositions. In connection with the impaction of calculi at the vesical orifice of the ureter, my colleague, Mr. Pitts, has favoured me with two most interesting cases of this condition:

A boy of 9 years was admitted to Great Ormond Street with symptoms of stone in the bladder, which was verified by the sound. On bimanual examination two stones were felt, one on each upper lateral portion of the bladder, that on the right side about the size of an almond and fixed, that on the left movable and of the size of a cherrystone. The suprapubic operation was performed and a stone removed of the size and shape of a plumstone. No other could be felt by the finger in the bladder, but, on repeating bimanual examination, a stone could be plainly felt in the position of entrance of the right ureter. Careful examination of this spot within the bladder revealed a protrusion of the mucous membrane, and, by probing the apex of this protrusion, a stone could be felt encysted in that part of the ureter which passes through the bladder wall. The mucous membrane was incised with scissors, and the stone, which was pyramidal in shape, made to project into the bladder by the finger of an assistant in the rectum. After very prolonged and careful manipulation it was finally loosened and extracted by aid of a bent director. It was about half an inch in its longest diameter, somewhat pyramidal in shape, with the apex projecting at the orifice of the ureter and the base firmly grasped by the surrounding structures. The wound united and the boy was discharged well in less than six weeks.

A second case which was under Mr. Pitts's care at St. Thomas's Hospital is of still greater interest and rarity. A thin cachectic child, aged 4 years, who had had symptoms of calculus vesicæ for two months, had been admitted to another hospital, where he was sounded under an anæsthetic, but nothing abnormal found. The child became much worse, and three months later came under Mr. Pitts's care. There was then retention

of urine, the bladder was distended to the umbilicus, the penis swollen, great pain complained of when catheter was passed, and the urine found to be very offensive, thick, and looking like pure pus, escaping very slowly through the catheter, in the eye of which a small stone was found. On April 6th a suprapubic incision was made. No stone was found, the wall of the bladder was much inflamed, the surface of the mucous membrane red and granular, with same indications of sacculation. A large drainage tube was inserted, and the patient placed in a boracic bath. This was changed for boracic irrigation on the sixth day, owing to signs of bronchitis. Six weeks later an attack of jaundice supervened, which was followed by inflammation of the right testicle and cord. On June 30th the tube was still in the bladder, and no urine coming through the penis, on July 18th an examination was made under chloroform. The bladder was found empty, but on rectal examination a hard nodular mass was felt on the left side between the rectum and the bladder. The cystotomy wound was enlarged, and an ulcerated opening was found in the trigone of the bladder near the neck, which led to a cavity outside the bladder, which contained four oval stones that were with difficulty dislodged and manipulated from the pouch into the bladder, and so removed. The largest of these calculi was of the size of a small plumstone. The boracic bath was repeated, and the child made a good recovery. Mr. Pitts adds as a note to this exceedingly instructive case, that in the absence of any stone on first opening the bladder, and from the suppurative condition found, together with the subsequent inflammation of the epididymis and cord, the condition was for a long time believed to be tuberculous. Hence the delay in the second operation, which resulted in finding the stones and curing the patient, a result which redounds to the credit of the surgeon.

Such cases as these admit of no other treatment than by the suprapubic operation, which was clearly indicated beforehand in all of them.

NOTE AND REFERENCE.

¹ *Clinical Journal*, 1896. ² The hospitals from which these statistics were kindly supplied were the Hospital for Sick Children (London), Children's Hospital (Pentlebury), the General Infirmary (Leeds), St. Peter's Hospital (London), Royal Hospital for Sick Children (Aberdeen), Royal Hospital for Sick Children (Edinburgh).

RECENT EVIDENCE AS REGARDS THE PRODUCTION OF SUGAR IN THE LIVER AND ITS UTILISATION IN THE TISSUES.

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THE busy practitioner frequently finds it no easy matter to weigh the value of the theories put before him, simply because he has not the time to study the evidence bearing upon the views advanced. For this reason it is the duty of anyone who presents his views to his professional brethren to state as clearly as possible all the evidence forthcoming, not merely the evidence derived from his own work, but of that derived from the work of others. It may be that in the opinion of the author the work is of no value, but he must at least give it consideration, and indicate where it is erroneous.

The universally-accepted views in regard to the action of the liver upon carbohydrates have recently been assailed, and my object in giving the following very brief account of some of the more important recent work upon the subject is to enable the practitioner to form an intelligent judgment upon a matter which bears so directly upon so important a question as the treatment of diabetes.

Briefly stated, the usually accepted glycolytic theory is:

1. That when there is an excess of carbohydrates in the food, the liver stores it as glycogen.

2. That in the absence of carbohydrates in the food, the liver converts its stored glycogen into sugar, and, when this is exhausted, forms sugar from other substances and passes it to the tissues.

3. That the sugar in the blood is used by the tissues.

Serious objections to these conclusions have been offered by only two investigators:

1. Seegen maintains that the liver does form sugar, but that the sugar is not formed from glycogen.

2. Dr. Pavy maintains that the liver stores carbohydrates as glycogen, but that it does not reconver this to sugar. He considers that the great function of the liver is to prevent sugar passing into the circulation, and that, if sugar does pass into the circulation, it is not used by the tissues but is simply excreted by the kidneys.

The evidence in favour of the production of sugar in the

liver and its utilisation in the tissues may be stated as follows:

A.—EVIDENCE OF THE FORMATION OF SUGAR IN THE LIVER.

1. Glycogen, under the influence of zymins, acids, micro-organisms, etc., is very readily converted to sugar. This alone is not an argument for the conversion of glycogen to glucose in the liver, since many processes which go on outside the body do not occur inside. But it is rendered of importance by the fact that this conversion does go on inside the body in various conditions.

2. Glycogen diminishes and glucose accumulates in the liver when the circulation through the organ is stopped.

3. After an animal has been killed there is at first a rapid and then a slower conversion of glycogen into glucose.

4. During the life of the animal many different conditions undoubtedly lead to the conversion of glycogen into glucose in the liver:

(a) Puncture of the floor of the fourth ventricle is known to cause a diminution of the store of glycogen in the liver, an increase of glucose in the blood, and the appearance of glucose in the urine.

(b) Pavy showed¹ that the passage of more highly oxygenated blood through the liver, and the inhalation of carbonic oxide,² caused the appearance of sugar in the urine. These latter observations have been confirmed by Araki.³ It is right to state that Garofalo denies that this occurs,⁴ while Straub⁵ maintains that the sugar is formed from albumen.

(c) Many drugs bring about a rapid conversion of glycogen to glucose in the liver. Among these may be mentioned strychnine and curare.⁶

(d) Stimulation of certain nerves and section of others causes the disappearance of hepatic glycogen and the increase of the sugar of the blood. The brothers Cavazzani⁷ show that the stimulation of the coeliac plexus causes the glycogen to diminish in the liver. If the circulation is stopped glucose accumulates; if the circulation is intact the glucose is, of course, carried away. In a less satisfactory series of experiments Morat and Dufourt⁸ show that stimulation of the spinal cord causes the disappearance of glycogen from the liver. The experiments of Levene⁹ tend to prove that stimulation of the vagus causes an increased production of sugar in the liver. Butte¹⁰ shows that stimulation of the peripheral end of the cut vagus increases the amount of sugar in the blood leaving the liver.

According to Dr. Pavy, all these examples of the conversion of glycogen to glucose are not to be considered as exaggerations of a normal process, but as due to the sudden development of a ferment or zymmin. This theory has been met by E. Cavazzani, who in his experiments on the change of glycogen to glucose brought about by stimulation of the coeliac plexus,¹¹ investigated whether the blood, coming from the liver, and the liver parenchyma showed any increase in their sugar-forming action as they should have done if a zymmin had been developed. No such increased action was found, and Cavazzani therefore concludes that the change must take place in the liver protoplasm, and is not due to a zymmin action.

Dr. Pavy's idea that a zymmin can suddenly develop in a gland which he says is not designed for producing an amylolytic zymmin¹² is difficult to comprehend when the evidence he adduces for the existence of such a zymmin in the liver at all times is considered. He holds that the liver after treatment with alcohol has a powerful amylolytic action. He seems to consider that this is due to the formation of a zymmin in the liver after death and not to the formation of a zymmin by the action of the alcohol. If the zymmin is formed after death, then treating the liver of a living animal with alcohol should yield a less powerfully amylolytic product than the treatment of the same liver after death.

The following experiment shows that no such increase in the amylolytic power of the liver occurs immediately after death, and that, if alcohol simply fixes a pre-existing zymmin, that zymmin is just as abundant in the living liver as in the liver after death:

A cat was chloroformed and the abdomen was opened, and one-half of the liver was excised, plunged in alcohol, and minced, and then pounded. The remainder of the liver was removed, kept for thirty minutes, and then treated in the same way. After twenty-four hours the alcohol was

poured off each, and the liver substance dried. One g. of each liver was placed in 20 c.cm. of solution of glycogen, and kept in the incubator for four hours and three-quarters. An equal portion was at once boiled. Glycogen was extracted by Kütz's method.

	Glycogen in Grammes.	
	Before Incubation.	After Incubation.
Liver during life	0.305	0.158
Liver after death	0.280	0.131

The idea of a production of a zymmin in the liver immediately after death is opposed by this experiment.

5. The amount of sugar in the blood of the hepatic vein is frequently greater than that in the blood of the portal vein.

If sugar is formed in the liver, it must under certain conditions—that is, when the supply of sugar from the food is cut off—be more abundant in the hepatic than in the portal blood. On the other hand, if the liver can take up and store sugar as glycogen, the difference may occasionally be the other way, and there may be less sugar in the blood coming from than in the blood going to the liver. Thus, in a very large number of cases, no marked difference is to be expected in the amount of sugar in the blood going to and in the blood coming from the liver.

Again, it must be remembered that the amount of blood passed through the liver is enormous, and that therefore very small additions of sugar to each cubic centimetre means an enormous supply of sugar to the circulation. These considerations are sometimes forgotten when the evidence as regards glycogenesis is being considered.

It is not my intention to consider the results of older experimenters. These I have already dealt with in a previous communication.¹³ But within the last few years certain investigations have been published bearing upon this debated point.

Butte¹⁴ gives a series of observations on the normal dog and on the dog kept without food, in which the peripheral end of the vagus was stimulated. In four experiments on the normal animal the average amount of glucose in the portal blood was 0.087 per cent.; in the hepatic blood 0.115 per cent.

6. The amount of sugar in the blood of the hepatic vein is, even in starving animals, greater than that in the blood in the arteries.

Mosse,¹⁵ working under Professor Zuntz, in order to obviate the objection that the sugar production in the liver was the result of operative procedure, left the abdomen unopened and catheterised the hepatic vein from the right jugular vein, and also bled the animal from the crural artery. The following are the results of his analyses of the glucose present, made by Allihn's gravimetric method. The dogs had starved for twenty-four hours:

No. of Experiment.	No. of Bleeding.	Sugar in 100 c.cm. of Blood.	
		Artery.	Hepatic Vein.
II. Dog	1	0.103	Lost
III. "	2	0.093	0.145
III. "	1	0.107	0.110
IV. "	2	0.147	Lost
IV. Sheep	1	0.070	0.052
V. "	2	0.040	0.072
V. Dog	1	0.058	0.070
VI. "	2	0.113	0.119
VI. "	1	0.050	0.071
VII. "	2	0.087	0.115
VII. "	1	0.145	0.132
VII. "	2	0.154	0.165
VIII. "	1	0.071	0.092
" "	2	0.075	0.101

Average:

Arterial blood	0.093
Hepatic vein	0.107

Thus even in dogs which had been without food for twenty-four hours there was a greater quantity of glucose in the blood leaving the liver than in the arteries.

7. The exclusion of the liver from the circulation diminishes the amount of sugar in the blood.

(a) Schenck¹⁸ showed that after bleeding there is an increase of sugar in the blood, but that this does not occur after exclusion of the liver by ligature, and that it is very small in starving animals, where, of course, the glycogen stored in the liver is small in amount.

(b) Tangl and Harley¹⁷ showed that, in dogs fed on flesh, ligature of the intestinal arteries diminished the amount of sugar in the blood. Here the supply of sugar from without was, from the nature of the diet, cut off before the operation, but it was only when the blood supply to the liver was interrupted that the amount of glucose in the blood fell.

Even in prolonged starvation the amount of sugar in the blood is not diminished. How, if the kidneys are constantly excreting it, and if it is not being constantly manufactured in the body, is this supply kept up?

B. EVIDENCE OF THE DISAPPEARANCE OF SUGAR IN THE TISSUES.

1. E. Cavazzani¹⁸ shows that after muscular work there is a diminution in the amount of sugar in the blood, and that this is not due to any increased action of a diastatic zym. The older experiments of Seegen and of Chauveau and Kaufmann had given similar results.

2. Vaughan Harley¹⁹ records the results of a series of experiments upon dogs which confirm the older investigation of Limpert and Falck, and of Brasol, that glucose when injected into the blood is not all excreted by the kidneys, and that, even when the ureters are ligatured and renal secretion thus stopped, the glucose rapidly disappears from the blood. This disappearance is not due to a storage as such in the tissues, or to a conversion to glycogen, and it is accompanied by a rise in the respiratory quotient, showing an increased oxidation. These experiments Dr. Pavy has not, so far as I am aware, considered, although they overthrow his most off-repeated argument in support of his theory.

3. F. Voit²⁰ records a series of experiments on the subcutaneous injection of various sugars in the human subject. Using a 10 per cent. solution, he finds that very large quantities can be administered without causing any disturbance. The simple sugars (monosaccharids) experimented with gave the following results:

		Injected.	Excreted in the Urine.
		Grammes.	Grammes.
Dextrose ...	...	100.00	2.64
" ...	...	60.60	Trace
" ...	...	11.24	None
Laevulose...	...	10.94	0.99
" ...	...	10.13	Trace
Galactose ...	...	9.23	0.16
" ...	...	9.58	Trace

These results with dextrose—ordinary blood sugar—are supported by the previous investigations of Leube,²¹ who found that in dogs the injection of 50 c.cm. of a 50 per cent. solution of dextrose caused no glycosuria. The disaccharids—cane sugar and lactose—sugars which do not normally pass as such to the circulation, but which are broken up into monosaccharids in the intestine, he found were entirely excreted by the kidneys.²²

These experiments are directly opposed to the statements made by Dr. Pavy at p. 188 of his *Physiology of the Carbohydrates*. These statements are based upon experiments in which an increase of the sugar of the urine was found to follow the injection of even small quantities of sugar into the blood. No attempt was made to ascertain whether all the sugar injected was excreted. In the face of the experiments of Harley and of Voit, the conclusion—which Dr. Pavy makes the most important proof of his theory of the physiology of the carbohydrates—cannot be considered satisfactory.

The evidence may therefore be considered as establishing:

1. That glucose is formed in the liver.
2. That glucose is used in the tissues and is not all excreted by the kidneys.

Dr. Pavy's theories, again enunciated in his supplementary Croonian Lecture, without any mention of the work of other investigators, are thus found to be

opposed by a large amount of careful work. Dr. Pavy ignores the fact that in his views he stands alone, and that he is attacking the position to which physiologists have been driven, not by the study of the investigations of one individual but by the consideration of a large amount of independent work. He must, therefore, be prepared to consider and refute the existing evidence before his views can be accepted by those who are capable of forming a judgment on the matter.

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- ¹⁷ *Journal of Physiology*, vol. xv, p. 130, 1893.
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PIGMENTED CELLS IN MOSQUITOS:

By SURGEON-MAJOR RONALD ROSS, I.M.S.

IN the *BRITISH MEDICAL JOURNAL* of December 18th, 1897, you did me the honour to publish an article by me on this subject, together with notes by Surgeon-Major Smyth, Dr. Manson, Mr. Bland Sutton, and Dr. Thin, on the original preparations. My sincere thanks are due to these gentlemen for the interest they have taken in the matter, and for the courtesy of their remarks, and I hope that the existence of the cells as attested by them may now be considered as established. As to the nature of the cells, however, doubt still remains, and I should therefore like to give two more instances in which they have been found, both having an important bearing on this point.

It will be remembered that the pigmented cells were not found in large a number of brindled and grey mosquitos, unfed or fed on healthy or crescent-bearing blood, but were seen for the first time in two large "dapple-winged" insects (Cases I and II) of a rare species, fed on crescent blood. Since then (September, 1897) I have observed them in two more insects. Case III: Some scores of small dapple-winged mosquitos, unfed or fed on healthy blood, had been examined without finding the cells. At last two of this species were persuaded to feed on a patient with crescents. One of them was killed next day; no pigmented cells could be found. The second was killed forty-eight hours after feeding; numerous pigmented cells were present. They were all small, much smaller than epithelial cells, ovoid, about 7 μ in the major axis, and each contained about 20 granules of typical pigment which were often arranged circumferentially, just as in the malaria parasite. No more insects of this species fed on malarial blood have since been examined. Case IV: A hundred or more grey or "barred-back" mosquitos (wings, legs, belly plain; back of abdomen transversely striated) unfed, or fed on healthy or crescent blood, have been dissected without finding the pigment cells. At last one was observed feeding on a patient whose blood that morning had been seen to contain numerous mild tertian parasites. I judged for many reasons that it had been feeding occasionally on the same man for several days. It was killed three days afterwards, when it must have been quite a week old (after hatching from pupa). Its stomach contained a large number of pigmented cells of all sizes, from 8 μ to 25 μ . They were very defined and distinct, especially the larger ones, and contained each from 10 to 20 granules of typical pigment. Some of the largest cells appeared to have a uniform structure without vacuoles, but with a central nucleus (?).

I thought I observed a few similar bodies without any pigment. Besides these cells the stomach cavity contained numbers of swarm spores, never before seen in any Secunderabad mosquito, but found in the mosquitos of the malarious Sigr ghat. In May a number of these swarm spores had been given to a person who volunteered to drink them, and he had been attacked with fever five days afterwards. I could trace no connection between the pigmented cells and