according to function. There we have a mystery, and yet it is a mystery we must recognise as an indication of fact. Function must be related to the chemical and molecular constitution of the nerve elements. The difference in susceptibility to different forms of force must depend on atomic constitution and molecular arrangement. We cannot conceive that the nerve endings in the skin which produce a nerve impulse on the slightest touch are quite the same in constitution as those which produce a nerve impulse when warmth is applied. We cannot believe that the same kind of structure can subserve the susceptibility to the massive motion of a touch or to the wave motion, only a little less frequent than the waves of light, which constitutes heat. And that difference, we can understand, is equal or greater in the motor and sensory terminal structures on which toxic influences for the most part primarily act. This enables us to understand why it is that poisons act specially upon structures with certain functions, and should even act first on one set of sensory nerves and not on another set. So we have, from different poisons, different effects upon the nerves, and we have also different effects from the same poison, probably dependent on the fact that it enters the blood in a somewhat different form, or with greater or less rapidity, and thus is assimilated by and deranges certain structures rather than others. Thus we have, from arsenic, palsy of the extensors of the arms and feet, as we have from alcohol. We have sometimes a perfect simulation of tabes, ataxy, muscular anæsthesia, and loss of knee-jerk, in consequence of the preponderant affection of the afferent muscle nerves, and sometimes we have chiefly sensory cutaneous symptoms, although scarcely ever without loss of the knee-jerk. Remember, that loss of the knee-jerk only indicates affection of the afferent muscle nerves, and that we know that the impairment of these nerves has many causes. To all toxic influences they seem specially susceptible.

Hence, I beg you to remember, above all things, as a practical rule, that whenever you have bilateral disturbance of the peripheral nerves, symmetrical, with a distinct limitation to function, sensory or motor, it is almost certainly due to a blood state. There is reason to believe that the degenerations which may appear to constitute an exception are really due to a blood poison. Many are the cases in which the recognition of that fact will save from grave error.

In the nerve symptoms of this patient there is little more for you to observe than I have told you, but if you ascertain for yourselves the absence of the knee-jerk, the fact may be more securely fixed in your mind, and it cannot be too surely held. But, as regards the cutaneous symptoms, there is a picture for you to study such as you will not see again. This arsenical pigmentation is so characteristic that the moment I saw it I was sure of its nature, but I never like my own certainty to be without corroboration if it is outside my own special region. So I sent the case to Dr. Radcliffe Crocker, and he is also absolutely certain. He has seen, he said, one more intense case, and he has kindly allowed me to show you a plate from his *Atlas*, which illustrates it.

I have myself become familiar with the pigmentation that is caused by arsenic because I have often seen it in the cases of epilepsy. I have also seen it in well-marked form, in a lady whose love for working on muslins led her to their continuous handling, and she preferred æsthetic tints. The result was that she began to suffer from pains that were ascribed to gout, until there came progressive palsy of the extensor muscles of arms and feet. This showed a toxic influence, by the symmetry and limitation I have mentioned. Then the pigmentation was discerned, although, I believe, chemical analysis had already made certain the cause. But the troublesome pustular eruption which bromide causes in most persons can only be prevented, or kept down to insignificant degree, by arsenic. No other drug, no modification of the way or form in which bromide is given, has any influence. Some patients are peculiarly prone to the rash, and have to take the drug for a long time; they have to take arsenic also. A slight degree of pigmentation is often produced in such cases. It has, therefore, several times happened to me that I have had to put to the patient the two evils, and say, "Which will you have, the spots or the pigmentation?" There is no other help for it; they must have one or the other. They always choose the pigmentation. It does not, however, increase to

a really serious degree in such cases, and I have not met with any other symptoms of chronic arsenical poisoning in consequence of the use of arsenic to prevent the bromide rash.

If you observe carefully the skin of this patient, you will see that the pigmentation begins as small round spots which seem to increase in size and coalesce, but leave small rounded areas of unpigmented skin. These appear whiter than normal, perhaps only by contrast. The pigmentation is abundant everywhere, but extreme on the neck, front and back of the trunk, arms, and thighs. For the most part it appears a simple deposit of pigment, dark brown in tint. But in many places you will observe small round spots of congestion, of the same size, which suggest that, at least when the process is going on actively, congestion may be the first part of the process. Moreover, in the neck, where the skin has been subjected to habitual friction, the pigmentation is so intense as to be practically continuous, and with it so much congestion is combined as to give the pigmented area a reddish or purplish-brown aspect. The congestion is also conspicuous on the hands, and there, on the palms especially, the spots are attended with distinct elevation. Indeed, where the epidermis is thick, there are minute raised elevations, at which no indication of congestion or pigmentation can be discerned.

The great fact is the pigmentation, at first essentially punctate or in small spots. It is that that is so characteristic. You will at once understand how important it is to be able at once to recognise a sign so distinctive and so significant. You cannot note the state too carefully. Once firmly fixed in the visual memory, it will not be lost. It is seldom easy to retain an image securely from a single opportunity of inspection, but this condition is one, I think, which you are not likely to mistake when you see it again. You may have some other opportunity of observing a similar condition. You probably will have such if you carefully examine the skin of patients who have been, for long, taking arsenic with bromide. But the story of the origin of this patient's illness suggests that a careful inspection of the skin of a number of men employed in shops where paints and papers are sold might afford an inquiring student opportunities of observing the pigmentation, which would be beneficial not to himself alone. It is certain that the change in the skin may long precede any other symptom.

Having helped you so far, gentlemen, I must now ask you to help yourselves. Observe, also, what I have not mentioned, the bilateral symmetry of the rash, a feature that you will recognise, from what I have said, to be inevitable. Connect it with the bilateral pains and loss of knee-jerk, and fix these features of limitation and symmetry in your minds in association with the toxic cause. For a moment, indeed, forget what the cause here is; forget the precise character of the symptoms, in order that the general facts of combined functional limitation and bilateral symmetry may stand out more clearly in your view, as landmarks which, whenever and wherever they are seen, will always guide you surely.

THE CROONIAN LECTURES

ON

A NEW DEPARTURE IN DIABETES.

Delivered before the Royal College of Physicians of London.

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[*Special Abstract Report.*]

LECTURE III.

AMOUNT OF SUGAR IN THE BLOOD.

AFTER recapitulating briefly the arguments of the two opening lectures, Dr. Pavy proceeded to state the result of his investigations as to the amount of sugar in the blood under normal conditions. This he said was in the general circulation very small. The results from upwards of 100 determinations of the amount of sugar present under natural conditions in various animals showed a range of from about 0.6 to 1.0, or a little over 1.0, per 1,000. The cupric-oxide reducing power

found to exist was ordinarily that of glucose, and when not so was only slightly below it.

Blood at the Moment of, and after, Death.

Dog.	Sugar per 1,000 expressed as glucose.	
	Before Sulphuric Acid.	After Sulphuric Acid.
Blood from the cavities of the heart ligatured and excised instantly after death	0.850	0.876
Blood afterwards collected from the chest	2.180	2.237

The blood from the heart was obtained from its cavities after immediate ligature of the great vessels as soon as the chest was opened. The amount of sugar it contained was to be considered a normal constituent, and a similar amount was to be found in the blood of the vessels in all parts of the body with one significant exception—the portal vein. The blood collected from the chest after death contained admixture, and did not represent the condition of systemic blood.

FLUCTUATIONS IN THE AMOUNT OF SUGAR IN THE PORTAL BLOOD.

Whereas the amount of sugar in the blood of the systemic circulation was constant, or nearly constant, that in the portal blood presented notable fluctuations in relation to food. In a fasting dog the amount of sugar in the portal blood was pretty nearly the same as in the blood of the general circulation. In the rabbit this was found not to be the case, the reason being that in a rabbit kept without food the process of digestion of the last meal went on very slowly, so that at the end of 24, or even 48 hours, the stomach still contained undigested food. Consequently even after these periods absorption was still going on, a fact which accounted for the greater proportion of sugar in the portal blood than in the blood of the general circulation, even when the animals had fasted for some time.

PORTAL BLOOD.—Amount and Nature of Sugar after Stated Periods of Fasting.

Animal.	Duration of Fast.	Sugar per 1,000 expressed as Glucose.		Cupric-Oxide reducing Power of the Sugar present in Relation to that of Glucose at 100.
		Before Sulphuric Acid.	After Sulphuric Acid.	
Dog ...	48 hours, nearly	0.580	0.643	90
Dog ...	" "	0.666	0.710	94
Rabbit...	24 hours, fully	1.583	1.733	91
Rabbit...	" "	2.454	2.499	98
Rabbit...	" "	2.244	2.244	100

The analytical results showed that the kind of sugar found in the portal blood, whether after fasting or after a diet of animal or of starchy food, was one possessing a cupric-oxide reducing power below that of glucose as a rule, and sometimes considerably below. The amount of sugar found in the portal blood after animal food was contrasted with that found after starchy food in tables from which the following are extracts. From these it would be seen, not only that the amount of sugar in the portal blood after a starchy diet was larger than after a meat diet, but that the sugar was different in kind, being further from glucose and nearer to maltose. This would appear from a comparison of the third column of figures, which gave the cupric-oxide reducing power of the sugar present to that of glucose at 100.

PORTAL BLOOD.—Amount and Nature of Sugar after Diets Stated.

Animal.	Hours after Last Meal.	Sugar per 1,000 expressed as Glucose.		Cupric-Oxide reducing Power of the Sugar present in Relation to that of Glucose at 100.
		Before Sulphuric Acid.	After Sulphuric Acid.	
ANIMAL FOOD.				
Dog ...	4	1.117	1.340	83
" ...	4	0.893	1.087	82
" ...	6½	0.633	0.683	93
" ...	5½	0.593	0.660	90
Cat ...	5	0.851	1.139	77
" ...	5	0.675	0.779	87
STARCHY FOOD.				
Dog ...	3½	1.183	1.477	80
" ...	2	0.977	1.100	89
" ...	1	0.968	1.277	76
Rabbit.	Short	1.407	1.707	82
" ...	2	2.587	3.234	80
" ...	3	2.346	2.878	82
" ...	4	1.630	2.085	78
" ...	4½ to 5	3.665	4.102	89
" ...	5 to 5½	1.461	1.657	88
" ...	5 to 5½	1.693	1.698	99
Maltose injected into stomach.				
Dog ...	25 min.	1.600	2.200	72

To ascertain if cane sugar passed as such into the portal blood, it was necessary in the process of analysis to use citric instead of sulphuric acid. The inference from the results given in the following table was that carbo-hydrate from ingested cane sugar reached the portal blood as glucose, and not in the state of cane sugar.

PORTAL BLOOD.—Amount and Nature of Sugar after Injection of Cane Sugar.

Animal.	Minutes after Meal.	Sugar per 1,000 expressed as Glucose.	
		Before Citric Acid.	After Citric Acid.
Dog ...	30	1.333	1.333
" ...	30	2.113	2.113

SUGAR IN THE BLOOD OF THE SYSTEMIC CIRCULATION.

If the fluctuations in the amount of sugar observed in the portal blood were transmitted on to the general circulation sugar would be passed in considerable quantities in the urine after each meal. According to the glyco-genic doctrine sugar derived from the liver reached the systemic capillaries, and was there destroyed or utilised in some way which had not been explained. As a matter of experimental observation, however, it did not thus disappear. A series of eleven observations, made some years ago by Dr. Pavy on the amount of sugar in the blood on the arterial and on the venous side of the capillaries, revealed a difference of only 0.003 per 1,000; the excess was on the side of the arterial blood, but results so closely agreeing afforded no tangible evidence that the sugar of the blood was destroyed in its passage through the systemic capillaries.

POSITIVE EVIDENCE AGAINST THE GLYCOGENIC DOCTRINE.

The negative evidence against the glyco-genic doctrine had been shown to be strong: (1) The liver at death was not more saccharine than other organs of the body; (2) the blood flowing from the liver was not more saccharine than that flowing to it, but the contrary; (3) there was no evidence of destruction of sugar in the systemic capillaries. Positive evidence against the theory could be advanced also. The kidney contained the same kind of blood as the other organs of the body supplied by the general circulation, and it was a most delicate and sensitive indicator of the amount of sugar in the blood. Though the quantity was small, there could

no longer be any question that sugar was a constant constituent in urine. Osazone crystals could be got from the urine of healthy men and animals, and the sugar was recoverable from these crystals.¹ The amount of sugar in healthy urine was in correspondence with that in healthy blood. If the amount of sugar in the blood were increased the amount of sugar in the urine was increased to a corresponding extent. The condition of the urine as to sugar therefore represented the condition of the blood as to sugar.

THE KIDNEYS AND THE EXCRETION OF SUGAR.

It had been asserted that the kidneys had a point of tolerance as to sugar in the blood, that is, that if the proportion of sugar in the blood was below a certain amount it was not passed off by the urine. The proportion had even been stated, and it was asserted that sugar first appeared in the urine when the quantity in the system exceeded 1 gramme per kilogramme of body weight. Dr. Pavy's experiments failed to support this proposition of Bernard's as to the tolerating capacity of the system for a certain amount of sugar. On the contrary, the results, as shown by the table which follows, were such as might naturally be looked for after the introduction of a diffusible substance, such as sugar, into the blood. There was in fact a notable rise in the amount of sugar in the blood at once, a fall in the amount after half an hour, and a still further fall after an hour, but at the same time a large amount of sugar was passed off by the urine. This rise in the amount of sugar in the urine was observed after the injection (into the jugular vein) of an amount of glucose equal to 0.5 gramme per kilogramme of body weight, not less distinctly than after the similar injection of 1 gramme per kilogramme of body weight, though the actual quantity was less. In a similar manner the injection of lævulose was followed by an increase in the amount of sugar first in the blood and then in the urine.

Amount of Sugar in the Blood and Urine at stated Intervals after Injection of Sugar into the Jugular Vein.

Animal.	Interval after Injection.	Cardiac Blood.		Urine.	
		Sugar per 1,000 expressed as Glucose.		Sugar per 1,000 expressed as Glucose.	
		Before Sulphuric Acid.	After Sulphuric Acid.	Before Sulphuric Acid.	After Sulphuric Acid.
		1 g. glucose per kilo. of body weight.			
Rabbit	At once	5.050	5.000		
"	30 mins.	2.450	2.703		
"	60 "	1.460	1.666	55.160	55.160
"	90 "	1.243	1.533	11.370	21.150
		0.5 g. glucose per kilo. of body weight.			
"	At once	2.380	2.548		
"	30 mins.	1.573	1.573		
"	60 "	1.390	1.370	11.370	17.860
		1 g. lævulose per kilo. of body weight. ²			
"	At once	4.387	3.787	3.571	6.250
"	30 mins.	2.523	2.577	97.402	71.091
"	60 "	1.893	1.800	37.037	35.333
"	90 "	1.603	1.517	30.303	25.900

An examination of these experimental results showed that even small amounts of sugar in the general circulation were not tolerated, but were passed off by the urine, and further that the sugar in the urine was of a different nature to that injected. If glucose were injected subcutaneously (in the rabbit) it was excreted by the kidney in a form possessed of a lower cupric-oxide reducing power than glucose. A possible source of fallacy in the experiment might be the presence of "animal gum" in the urine, but experiments devised with the object of precipitating the animal gum gave results which revealed the same kind of difference, thus rendering

it evident that the sugar present in the urine had in reality a lower cupric-oxide reducing power than glucose. It was a sugar of this type which existed in healthy urine, whereas in diabetes the sugar present was glucose.

Nature and Amount of Sugar in the Urine after the Subcutaneous Injection of 1 g. Glucose per Kilo. of Body Weight.

Animal.	Sugar by 1,000 expressed as Glucose.		Cupric-Oxide reducing Power of the Sugar eliminated in Relation to that of Glucose at 100.
	Before Sulphuric Acid.	After Sulphuric Acid.	
Rabbit...	48.08	67.79	73
" ...	19.84	51.89	38
" ...	39.68	94.46	42
" ...	34.72	69.44	50
" ...	21.74	35.72	61
" ...	10.41	19.23	54
" ...	48.78	110.85	44

The urine was obtained from the bladder about two hours after the injection.

THE URINE AND BLOOD IN DIABETES.

The phenomena observed in diabetes presented a further illustration of the fact that the condition of the urine was representative of that of the blood. A certain amount of sugar was always present in the blood, and therefore in the urine. If the amount of sugar in the blood were increased, that in the urine rose also. Sugar present in the blood to the amount of 2 per 1,000 represented a strongly saccharine state of the urine. These points were illustrated by the following analyses of the amount of sugar in the blood and in the urine of four cases of diabetes. Cases I, II, and III were examples of the severe form of diabetes; Case IV was of a milder type, and the amount of sugar passed under a partially-restricted diet was less than that passed under a restricted diet in the other cases.

Comparative States of the Blood and Urine in Diabetes.

Case.	Date.	Diet.	Urine Sugar per 1,000 Parts.	Blood Sugar per 1,000 Parts.
I	Jan. 5	Mixed	109.91	5.763
II	" 8 " 28	Mixed Restricted	94.08 61.34	5.545 2.625
III	June 8 July 20	Mixed Restricted	93.39 45.49	4.970 2.789
IV	March 9 June 28	{ Partially Restricted }	48.11 31.76	1.848 1.543

If the liver permitted the blood of the general circulation to present the fluctuating condition observed in the portal blood, or if it poured sugar into the blood, as was said, then there would be a condition of diabetes. The liver, in fact, did exactly the reverse of what it was supposed to do under the glycogenic theory; its function was, in fact, to prevent carbo-hydrate reaching the tissues in a free state.

A UNIVERSITY SETTLEMENT IN BATTERSEA.—On June 24th—the anniversary of the laying of the foundation stone of the present building—a number of old Caians in London visited the Caius Mission and Settlement in Battersea. During the past two years over £2,000 has been contributed, and with this sum the buildings already erected have been paid for and ground for future extension acquired. The work of the Mission is carried on under the direction of the Warden, the Rev. W. B. L. Hopkins, by members of Caius College, as a rule medical students who have left Cambridge for London, and are willing to give up part of their spare time to forward the purpose of the Mission, which, over and above religious instruction, includes weekday meetings for lectures, debates, ambulance, nursing, and musical classes.

¹ Specimens of such crystals from the urine of man, the horse, and other animals were shown at the conclusion of the fourth lecture.

² The fall in the amount of sugar occasioned by boiling with sulphuric acid was in harmony with the known property of lævulose to be more easily destroyed or lost by the action of heat and acids than dextrose.