A CRITICAL REVIEW OF THE CEREBROSPINAL FLUID SUGAR.

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TECHNIQUE.

IN the series of 151 readings submitted we have estimated the spinal fluid sugar content by the method of Folin-Wu, as modified for the spinal fluid after deproteinisation with tungstic acid. In the majority of cases the estimation was performed within one hour of the collection of the fluid, but in some instances the examination was unavoidably delayed, even up to as much as 12 hours after collection. Glycolysis is usually stated to occur rapidly in spinal fluids kept at room temperature unless the fluid has been previously deproteinised, and in cases where specimens have to be conveyed to a laboratory from outlying districts erroneously low readings may result. It may therefore be advisable in some instances, where scientifically accurate readings are desired, to deproteinise such specimens before transit to the laboratory. In our opinion glycolysis only occurs with sufficient rapidity to negative the clinical value of the estimation in fluids with a high protein content, and in fluids from cases of meningitis in which pyogenic bacteria are present, providing that not more than 12 hours elapses between collection and examination. As the majority of specimens received in a general laboratory do not fall, under ordinary circumstances, within either of these categories, we see no reason for discarding specimens as valueless because of some delay in transit. In support of our contention we append the results of duplicate sugar estimations on 14 unselected samples of spinal fluid. The sugar content was determined on a part of the specimen immediately upon its arrival at the laboratory. An untouched fraction of the same fluid was then allowed to stand for about 12 hours on the laboratory bench at room temperature, after which time its sugar content was again estimated.

<i>Diagnosis.</i>		<i>Protein in mgm. %</i>		<i>Sugar (1) in mgm. %</i>		<i>Sugar (2), after 12 hours, in mgm. %</i>
Uræmia		200		167		154
G.P.I.		125		60		57
G.P.I.		100		72		64
Epilepsy		100		75		74
Spinal Syphilis		75		80		76
Encephalitis		75		91		87

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<i>Diagnosis.</i>	<i>Protein in mgm. %</i>	<i>Sugar (1) in mgm. %</i>	<i>Sugar (2), after 12 hours, in mgm. %</i>
Undiagnosed	75	69	64
Disseminated Sclerosis	50	64	64
? Spinal Tumour	50	67	67
Cerebral Tumour	50	69	63
Sinusitis	50	71	71
Sinusitis	30	91	91
? Diabetic Coma	30	83	80
Congenital Syphilis	25	57	54

The protein content, as total protein, was estimated by Young and Bennett's¹⁸ method on each specimen immediately after its arrival in the laboratory.

The number of observations on which to base an opinion is small, but we believe that glycolysis is not, in general, as rapid as it is frequently stated to be.

PREVIOUS OBSERVATIONS.

Greenfield and Carmichael¹⁰ place the normal variations in the spinal fluid sugar from 45 to 85 mgm. per cent. They state that an increase is usually the reflection of an increase in the blood sugar, and that a hyperglycorrhacia is therefore to be expected in :—

1. Diabetes mellitus with hyperglycæmia. In these cases the spinal fluid sugar is commonly from 100 to 250 mgm. per cent. In diabetic coma figures from 300 to 600 mgm. per cent. have been noted.

2. Nephritis. In uræmia values of 145 to 200 mgm. per cent. have been obtained.

Apart from these two diseases, the authors state that it is probable that the spinal fluid sugar never exceeds 100 mgm. per cent. A slight increase may be observed in states of raised intracranial pressure from any cause. They also state that a decrease, amounting even to actual disappearance of sugar from the fluid, is seen in cases of tuberculous and 'purulent' meningitis. In tuberculous meningitis the sugar values may range from 11 to 50 mgm. per cent. In 'purulent' meningitis any values may be obtained from low normals down to complete absence.

Goodwin and Shelley⁹ conclude that :

1. The spinal fluid sugar content is not constant for the same person.
2. There is no level within reasonable limits that might be considered normal for different individuals.
3. There is a definite relationship between the sugar content of the spinal fluid and the blood. This may be expressed as a percentage relation of the spinal fluid sugar to the blood sugar. The figure obtained in normal cases is fairly constant within the limits 45 to 65 per cent.

4. Ingestion of carbohydrates in sufficient quantity causes a definite and constant rise in the spinal fluid sugar, and disturbs the usual relationship between the spinal fluid and the blood sugar.

5. Meningitis, either tuberculous or 'purulent,' frequently gives rise to a low spinal fluid sugar reading, both as regards the actual content in the spinal fluid and in relation to the blood sugar.

Crawford and Cantarow⁵, as the result of the study of 210 cases, state among other conclusions that "great increase in globulin and high sugar content are characteristic of increased intracranial pressure in general, and particularly of brain tumour. High sugar values are also obtained in various mental disorders. The essential cause of hypoglycorrhacia is glycolysis, which occurs to a large extent in acute suppurative meningitis, and to a slight degree in tuberculous meningitis. Sugar determinations are of great value in the differential diagnosis of tuberculous meningitis, especially from epidemic encephalitis."

Spurling and Maddock¹⁴, using the Folin-Wu method of sugar estimation, found no significant variation in the sugar content of the spinal fluid in cases of brain tumour. The sugar values varied in their series from 57 to 84 mgm. per cent., with an average of 74 mgm. per cent.

Halliday¹¹, estimating the spinal fluid and blood sugar by MacLean's method, concludes that :

1. In epidemic encephalitis the fasting level of the blood and the spinal fluid sugar is within normal limits, the fasting level of the spinal fluid sugar being lower than that of the blood sugar.

2. Associated with the physiological blood sugar curve is a corresponding spinal fluid sugar curve. The latter is a delayed curve, and the non-recognition of its existence may have been responsible for the high spinal sugar findings obtained by many workers in encephalitis and other allied conditions.

3. A specimen of spinal fluid to be estimated for its sugar content should be collected after a 12 hours' fast, coincidently with a sample of blood for a similar investigation. If the sugar content of the spinal fluid is normal its ratio to the blood sugar should lie between 50 and 70 per cent.

4. Specimens of spinal fluid at varying intervals after a meal give sugar readings which are valid only when these readings are correlated with the complete sugar curves, both of the blood and spinal fluid.

In a series of 25 cases, of which 20 were cases of encephalitis, Halliday obtained the following figures for the blood and spinal fluid sugar, estimated on specimens taken after a 12 hours' fast. The blood sugar varied from 68 to 128 mgm. per cent., the average figure being 95 mgm. per cent. These figures correspond with those given by MacLean, 80 to 128 mgm. per cent., as normal for the fasting level in a healthy person. The spinal fluid sugar ranged from 42 to 70 mgm. per cent., the mean being 56 mgm. per cent.,

Cookson³, in a small series of readings, found that "in almost every case diagnosed finally as encephalitis lethargica the sugar content was definitely increased above the normal, and that in no instance was there any diminution."

Bourges, Foerster and Marcandier², quoted by Halliday, in a series of 6 cases of epidemic encephalitis, found a hyperglycæmia associated with a hyperglycorrhæcia. This increase they considered to be a valuable aid in diagnosis. The methods of estimation employed were not stated, and they accepted as the normal sugar content of the spinal fluid Mestrezat's figure of 53 mgm. per cent.

Foster⁶, quoted by Halliday, using the Folin-Wu method, and accepting for the average normal spinal fluid sugar reading the figure of 53 mgm. per cent., obtained values ranging from 53 to 113 mgm. per cent., with an average of 76 mgm. per cent., in a number of fluids examined. He concluded that the spinal sugar was increased in encephalitis, but he could not find any corresponding increase in the blood sugar.

Thalheimer and Updegraff¹⁶, quoted by Halliday, using Benedict's method of sugar estimation, found both a hyperglycæmia and a hyperglycorrhæcia present in encephalitis. Their figures, even for the normal blood and spinal fluid, are extraordinarily high. Most of the specimens were collected coincidentally after 12 hours' starvation.

Foster and Cockrell⁷, quoted by Halliday, using the Folin-Wu method, and considering the normal spinal fluid sugar to lie between 40 and 60 mgm. per cent., found readings over 60 mgm. per cent. in 34 out of 35 cases of encephalitis. Similar high values were obtained in other pathological states such as brain tumour, gas poisoning, septicæmia and tabes. They considered that the increase in the spinal fluid sugar in encephalitis, though not confined to that condition, was useful in making a diagnosis.

Coope⁴, using the Folin-Wu method, examined 11 cases of encephalitis and found 9 with a spinal fluid sugar over 60 mgm. per cent., but of 69 specimens from other diseased states, mainly insanities, 60 also gave values over that figure. He concluded that "the French tendency to regard a high sugar content of the spinal fluid as in favour of lethargic encephalitis does not appear to be justified, as figures quite as high occur in other nervous diseases."

Stowe¹⁵, in a series of 122 cases, found that 15 cases of neurosyphilis gave values of 60 to 91 mgm. per cent., thus showing no departure from the normal, since he places the normal limits of variation of the spinal fluid sugar between 60 and 90 mgm. per cent. Of 20 cases of encephalitis lethargica only two showed any abnormality; in both cases the figure was high. Twenty-one cases of proved tuberculous meningitis had a sugar content varying from 10 to 50 mgm. per cent., and 14 cases of purulent meningitis yielded values ranging from 0 to 25 mgm. per cent.

Alpers, Campbell and Prentiss¹ examined 421 spinal fluids from normal cases, epidemic encephalitis, general paresis, dementia præcox, manic-depressive insanity and various miscellaneous conditions. They employed the Benedict-

Osterburg method for the estimation of the urinary sugar, modifying it to suit their own particular requirements. A control estimation was made in each case by the Folin-Wu method. They placed the normal range of the spinal fluid sugar between 50 and 65 mgm. per cent. In epidemic encephalitis the average figure obtained was 82 mgm. per cent., an increase which they consider to be of some diagnostic value. Twenty-one cases of dementia præcox yielded an average figure of 80 mgm. per cent., but high readings were less often obtained than in the cases of encephalitis. In general paresis and manic-depressive insanity the sugar readings fell within the normal limits of variation.

Purves-Stewart¹³ states that an excess of sugar is often found in the spinal fluid in cases of epidemic encephalitis, in marked contrast with the two chief conditions with which the disease is likely to be confused, viz., tuberculous meningitis and early poliomyelitis.

Fremont-Smith and Dailey⁸ conclude that the cerebrospinal fluid and the blood contain reducing bodies other than glucose. Sugar tolerance curves in the blood are followed after a latent period by a similar variation in the spinal fluid, and the spinal fluid sugar may be at one stage higher than the blood sugar. Spinal fluid sugar values above 80 mgm. per cent. occur in a great variety of conditions beside encephalitis lethargica. Such high values are usually associated with a hyperglycæmia, which is a not uncommon concomitant of cerebral lesions. In the absence of a hypoglycæmia, spinal fluid sugar readings below 50 mgm. per cent. nearly always signify acute infection of the meninges. Values between 50 and 80 mgm. per cent. occur in the normal, in many metabolic diseases, in acute meningeal infections, encephalitis lethargica, brain tumour and syphilis, etc. The authors consider that the spinal fluid sugar should be determined on fasting patients and compared with the coincident blood sugar.

Wilcox, Little and Hearn¹⁷ conclude that the spinal fluid sugar should always be estimated in relation to the blood sugar. The normal relative value varies from 40 to 60 per cent. of the blood sugar. High relative values are found consistently in epidemic encephalitis, meningismus, convulsions, acidosis and nephritis, in poliomyelitis of the bulbar type, and in a certain number of so-called normal cases. From the variety of cases in which a high relative reading is obtained it is evident that this is not a reliable diagnostic test. Low relative values are encountered in acute purulent and tuberculous meningitis with great regularity, and this finding is of considerable diagnostic importance.

Levinson¹² concludes from the study of a small series of fluids that, for clinical purposes, there is no especial advantage to be derived from the determination of the sugar values on coincident samples of blood and spinal fluid. He found that the sugar content of various meningitic fluids examined ranged from 45 mgm. per cent. down to a mere trace, that the figures varied from day to day, and that the spinal fluid sugar bore no direct relation to the blood sugar, which, in the same series of cases, ranged from 84 to 176 mgm. per cent.

DISCUSSION.

A review of recent work on the spinal fluid sugar and its diagnostic value reveals, amid many contradictions, a general agreement to the effect that the findings are constantly lower than normal in tuberculous meningitis, and that there is a further constant reduction in all cases of purulent meningitis, irrespective of the particular micro-organism responsible for the lesion. With regard to the diagnostic value of increased sugar readings, it is generally accepted that any state of hyperglycæmia is followed after an interval by a rise in the spinal fluid sugar content, but, in the absence of a hyperglycæmia, it appears doubtful whether high spinal fluid sugar values ever occur with sufficient consistency to be of any diagnostic significance. A hyperglycorrhæcia, without an accompanying hyperglycæmia, has been inconstantly observed in cases of brain tumour, epidemic encephalitis, and various other lesions of the central nervous system. We consider, from a brief review of the recent work on the subject, that there is no generally substantiated evidence that the spinal fluid readings, either alone, or in relation to coincident blood sugar readings, are of diagnostic value in epidemic encephalitis.

In our opinion, some of the contradictory observations upon the importance of the spinal fluid sugar figures in encephalitis may have arisen as the result of the differing values given by the various sugar-estimation methods in vogue. Estimations, by the same worker, of the sugar content of a single specimen of spinal fluid, performed in duplicate by the methods of MacLean and of Folin-Wu, yield almost invariably, in our experience, higher readings by the former method than by the latter. The same observation also holds true for the blood sugar. We are not prepared to discuss the relative accuracy of the various methods in use, but we do suggest that the confusion is liable to continue until such time as a single standard method of sugar estimation is in universal use. In addition there must also be a universally accepted normal range of variation of the spinal fluid sugar.

Recent workers, with the exception of Levinson, stress the importance of estimating the sugar content on coincident samples of blood and spinal fluid in order to obtain the spinal fluid—blood sugar ratio. While this ratio may be of scientific interest, it does not appear to us to confer upon the clinician any decided advantage over the actual spinal fluid sugar reading. The various investigators are not in complete accord as to the exact normal limits of variation of this ratio, and it has yet to be shown that the ratio presents a sufficiently constant figure for any one particular disease to warrant its routine application. There is ample confirmation that actual diminution in the spinal fluid sugar finding is significant of a meningitic lesion, of either tuberculous or pyogenic origin. In these diseases the blood sugar is usually not affected, and it exercises no influence upon the diagnostic significance of the spinal fluid figures per se.

It is, however, obviously of importance, in view of the demonstration of physiological sugar curves in the cerebrospinal fluid, to collect the specimen whenever possible after a period of fasting. In hospital practice this precaution can easily be ensured by collecting all the samples in the morning, after the night's fast, and before any further food has been taken. It is seldom that a case is so urgent that this procedure could not be adopted as a routine measure in hospitals and similar institutions. In private practice there are difficulties in the way of adopting this procedure, and it would therefore be of advantage in some private cases to take coincident samples of the blood and spinal fluid for sugar determinations.

Taking the figures 50 to 80 mgm. per cent. as the possible normal limits of variation in the spinal fluid sugar (figures arrived at after a study of the normality ranges advocated by the authorities previously quoted), we have encountered high sugar values in such diverse conditions as uræmia, cord tumour, congenital mental deficiency, hysteria, brain abscess, cerebral hæmorrhage, acute encephalitis, general paresis and disseminated sclerosis. In the accompanying Table we have plotted down the sugar values obtained in our series of estimations. A glance at the Table shows that the majority of the readings fall within the normal limits of variation, and that in only two diseases do the spinal fluid sugar values lie constantly and definitely outside the normality range. In both these conditions, tuberculous meningitis and acute purulent meningitis, there is a marked reduction in the sugar content of the spinal fluid. All the cases of tuberculous meningitis were proved either by the bacteriological finding of the tubercle bacillus in the cerebrospinal fluid, or by the pathological findings at the subsequent autopsy. In the majority of the cases both the bacteriological and the histological findings were available. Similarly, all the cases of acute purulent meningitis were proved by the isolation and cultivation of the infecting bacterium during life. In many of the cases the confirmative autopsy finding was also available.

In four of our cases of acute purulent meningitis and in two cases of tuberculous meningitis the spinal fluid sugar fell below 10 mgm. per cent., and in three of former cases it was probably entirely absent. There is a simple and satisfactory explanation for the reduction in the spinal fluid sugar in acute purulent meningitis, viz. that the bacteria present utilise the sugar in the course of their growth and multiplication, just as they readily utilise glucose in artificial culture media. It is doubtful whether this explanation is applicable in the case of tuberculous meningitis, since the tubercle bacillus does not evince any especial partiality for glucose in artificial culture. In connection with this fact it is significant that the spinal fluid sugar rarely drops below 10 mgm. per cent. in tuberculous meningitis.

All observers agree that a constant, definite hypoglycorrhæmia occurs in association with a tuberculous or pyogenic infection of the meninges, and

that, taken in conjunction with positive clinical evidence, a definite reduction in the spinal fluid sugar content is diagnostic of the meningitis. Our findings add further confirmation to the generally accepted opinion.

It will be seen from the Table appended that we have not observed the high sugar values in encephalitis lethargica that some other workers claim to have obtained. In our experience a hyperglycorrhacia does not occur with any constancy in encephalitis lethargica, providing that the upper limit of the normal variation in the spinal fluid sugar is placed at 80 mgm. per cent. Had we accepted the figure of 53 mgm. per cent. as the normal, it is obvious that our findings would have led us, erroneously we believe, to assume that a hyperglycorrhacia was present in encephalitis, though its significance would have been negated by a similar finding in other diseased conditions of the central nervous system. It has been suggested by certain observers that the finding of a hyperglycorrhacia is an important aid to the diagnosis of encephalitis lethargica. In our opinion the finding of a normal or high spinal fluid sugar is a valuable aid in the elimination of tuberculous meningitis, when a diagnosis of encephalitis lethargica is under discussion, but otherwise we do not believe that the estimation of the spinal fluid sugar offers a trustworthy short-cut to the diagnosis of the latter condition.

We regret that we have not had an opportunity of examining fluids from cases of syphilitic meningitis, or acute anterior poliomyelitis, since the readings, especially in the latter condition, would undoubtedly have been of interest.

SUMMARY.

1. One hundred and fifty-one estimations of the cerebrospinal fluid sugar have been performed, by the Folin-Wu method, on fluids from various diseased states of the central nervous system, and on fluids from individuals showing no evidence, clinically, of any involvement of the central nervous system.
2. The results obtained confirm the opinions of previous observers that a constant reduction, which possesses diagnostic value, is encountered in tuberculous and acute purulent meningitis.
3. A constant hyperglycorrhacia has not been observed in encephalitis lethargica, and the finding of an increased spinal fluid sugar is not believed to be significant of that condition.

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