series is two out of forty-two, or 4.7 per cent. Nineteen cases—that is, 42.2 per cent.—had a morbid puerperium. In sixteen cases the lower segment operation was performed, and of these seven, or 43.7 per cent., had a morbid puerperium.

No attempt has been made to follow up the subsequent obstetric history of these cases as a whole, but I have performed a subsequent Caesarean section on three of the patients—namely, V 2, VI 3, and the patient with the rigid cervix referred to in I. It is interesting to note that the first of these became pregnant again after nine months, and the other two after five months, suggesting that the infection had not been a very serious one. In the case of V 2 there was an adhesion between the omentum and uterus, but none to the abdominal wall or elsewhere. In the other two cases there were numerous adhesions.

Technique of Operation

The technique adopted in both infected and clean cases is the same in many particulars. Thus in all my cases the abdomen is painted with Bonney's blue paint, and the vagina swabbed out when the patient is anaesthetized. Pitocin (1 c.cm.) is injected into the uterine wall immediately the child is delivered. If the classical operation is performed the uterus is sewn up with interrupted

silkworm-gut stitches, and a continuous catgut suture superimposed. The additional precautions taken in infected cases when the classical operation is employed include some or all of the following: evisceration of the uterus before incising it, swabbing its cavity with Bonney's blue paint, suturing an omental patch over the uterine scar, and abdominal drainage.

A prophylactic injection of scarlatinal antitoxin is given in every doubtful case, and if the soft parts have been injured—as, for example, in V 2—*B. welchii* serum is given too. Many cases receive quinine injections in addition. I now employ the lower segment operation in almost every doubtful case, but I have only done this comparatively recently, and if it is permissible to draw any conclusions from such a short series the results from the lower segment operation would not appear to be any better than those from the modified classical operation. When the risk of infection seems to be very great a Caesarean hysterectomy is performed, and this was done twice in this series.

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VON GIERKE'S DISEASE ASSOCIATED WITH AMYLORRHOEA

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A medical rarity has its own interest. If it can be shown to illustrate a perversion of a well-known physiological mechanism its value becomes even greater, in that it may shed light upon normal metabolic processes as yet imperfectly understood. In von Gierke's disease glycogen accumulates in various organs of the body, especially the liver, and is only broken down with the greatest difficulty.

The condition was first described by von Gierke¹ in 1929; subsequently cases have been recorded in America,^{2, 9} Australia,^{10, 11} France,^{12, 13} Germany,¹⁴⁻¹⁸ Holland,^{19, 20} Italy,²¹ and in this country by C. Worster-Drought,^{6, 7} Bellingham Smith and O'Flynn,⁵ E. C. Warner,⁴ and R. W. B. Ellis.^{2, 3} Von Gierke's¹ original case occurred in a little girl aged 8. It was characterized by progressive enlargement of the liver without any enlargement of the spleen. There was no jaundice and no ascites. The child died from influenzal pneumonia. At the necropsy the liver and kidneys were found to be greatly enlarged and infiltrated with enormous quantities of glycogen. The liver contained as much as 10 per cent. of its post-mortem weight of glycogen, and, as Schönheimer showed, this glycogen failed to undergo hydrolysis when it was incubated at body temperature. More recently cases have been described in which the deposition of glycogen has not been confined to the liver and kidneys, but has occurred in other tissues, such as skeletal,¹⁹ heart,^{8, 19} pyloric stomach muscle,²⁰ or even the central nervous system.⁸

The disease is one of childhood. It seems likely that there is a tendency to slow spontaneous recovery providing that the child does not succumb to an intercurrent infection. Stunted in growth, though by no means necessarily backward mentally, the child has a well-covered and prominent abdomen, which is in striking

contrast with its thin and underdeveloped limbs. There is progressive enlargement of the liver, but not of the spleen. There is no jaundice or ascites. The fasting blood sugar is low, and is not appreciably raised by the injection of adrenaline. The glucose tolerance curve is abnormal. Acetone is present in the urine at some stage of the disease, and in some cases is a constant feature.

Hypertrophic steatosis of the liver, which resembles the condition so closely that Debré and his co-workers¹² decline to distinguish between it and von Gierke's disease and group the two conditions together under the heading "hépatomégalies polycoriques," follows an acute infection, and does not give rise to ketonuria. Our object in recording this case is to describe a new finding and to discuss its bearing on the pathology of the condition.

Clinical and Biochemical Findings

The patient was 5 years old, and presented all the typical features of the condition except that, so far from being fat, he was definitely thinner than normal. The liver was greatly enlarged, especially the right lobe, which was separated from the left by a "notch" (see illustration). His weight had been average at birth, but had only increased erratically. Every cold caught was followed by a period of stationary weight lasting for six months or more. In January, 1934, following a minor infection, he had what was apparently an attack of ketosis, since he was comatose, with marked air-hunger. He was very bright mentally, but walked late, and until recently used to become extremely exhausted after short walks or other similar exertion.

Biochemically the usual features were present.

1. The fasting blood sugar was 50 and 57 mg. per cent. respectively on two occasions.

2. The glucose tolerance curve was abnormal in that it rose to a higher level than normal and took a long time to come down:

Fasting blood sugar	...	...	...	50 mg. per cent.
Forty-five minutes after the ingestion of 1 gram glucose per kg. of body weight	...	...	...	175 " " "
Two hours after glucose	...	...	...	100 " " "

3. There was a deficient response to the injection of adrenaline.

Fasting blood sugar	...	...	...	57 mg. per cent.
Fifteen minutes after the injection of 5 minims of 1 in 1,000 adrenaline, blood sugar	...	...	...	60 " " "

4. The urine contained acetone in both the fasting condition and at the end of the glucose tolerance test, and in both instances its pH was 5.2.

So far the findings corresponded to what has hitherto been described, but the following seems to be a new observation. The patient's mother had been impressed by the fact that his stools had always been peculiar and jelly-like, and that when he was worse in health the stools were more abnormal. On analysis it was found that the fat was within normal limits:

Total fat	= 17 per cent.
Neutral fat + free fatty acids ...	= 10 " "
Soaps	= 7 " "

Under the microscope an enormous amount of starch was visible. Quantitatively it was found that 34 per cent. of the dried faeces was starch (estimated as glucose). This led at once to the suspicion that amylase was absent or deficient, but it was found that the faeces of this child

digested an artificially prepared solution of starch more readily than did the faeces of a normal child on the same diet.

One gram of the patient's faeces (wet) digested 120 c.cm. of a 1 per cent. solution of starch.

One gram of the normal faeces (wet) digested 44 c.cm. of a 1 per cent. solution of starch.

Discussion

Why did the amylase not attack the starch? A faecal extract was filtered through a Chamberland filter candle to get rid of the organisms, but the diastatic activity remained unchanged. Therefore the digestion that occurred when a mixture of the faeces and a solution of starch was incubated could not be attributed to bacterial activity, but must be due to the presence of active amylase. What prevented the amylase from digesting the starch when the faeces (containing both) were incubated? The only possibility seemed to be that the reaction was at fault, and this was found to be the case. The faeces which had been stored on ice before analysis were found to be highly acid in reaction, and only when the acids were neutralized by the appropriate addition of alkali did fermentation of the starch occur *in vitro*. It would appear, then, that in von Gierke's disease there is (1) inability on the part of the liver to convert animal starch (glycogen) into glucose, and (2) impaired digestion of vegetable starch in the intestine.

It is clear that the condition represents a profound disturbance of the carbohydrate metabolism. Glycogen is not utilizable; it accumulates as a waste product in the liver and other organs, and starch is imperfectly digested in the alimentary canal. It would be logical to assume that there is one single factor responsible for both these phenomena, but it is extremely difficult in view of the complex nature of the problem, involving as it does the interplay of enzymes, substrates, hydrogen-ion concentrations, and endocrine factors, to evolve a satisfactory working hypothesis.

Hepatic Dysfunction

Several interesting problems arise. Why is the glycogen not broken down in the liver?

1. There might be a lack of amylase (glycogenase) in the liver, as originally hypothesized by von Gierke. Unshelm¹⁵ showed this theory to be untenable. He incubated a mixture of the liver in von Gierke's disease with a solution of starch, and obtained rapid hydrolysis with the liberation of glucose.

2. Glycogenase might be adsorbed to protein material in the liver. Willstätter¹⁵ showed that leucocytes contained two kinds of amylases, "bound" and "free." The "bound" ones are relatively inert, since they tend to become adsorbed to proteins. It is possible that the amylases in the liver in von Gierke's disease are all in the "bound" form, and require some factor to liberate them. This is the view favoured by Unshelm.¹⁶

3. The fault may lie in the glycogen rather than in the enzyme. Unshelm,¹⁵ however, showed that if normal glycogen-free liver was minced up with von Gierke liver and allowed to incubate, the glycogen was broken down. Therefore in von Gierke's disease glycogen is not present in a form which cannot be hydrolysed in the liver by its own enzymes.

4. There is still the possibility of a local pH disturbance in the liver. It might be that in the liver cells the reaction is such that the glycogenase cannot attack the glycogen. In support of this view we would quote our own findings with regard to the faeces. Here the presence of undigested starch was associated with its high acidity, and not with any lack of ferment; probably the reaction in the immediate neighbourhood of the starch grains in the intestine was such that the amylase could not split the starch.

5. The immobilizability of glycogen may be due to a persistence of the foetal condition. This is the view held by the German school, and by van Creveld,¹⁹ who considers it to be a hormonal effect. The persistence of the foetal condition might well be invoked to account for the amyloirrhoea in this case, since it is known that starch is not readily digested during the first few months of infancy.

6. Is the condition due to an endocrine disturbance? There is considerable experimental and clinical evidence in favour of this view. The low blood sugar, the abnormal glucose tolerance curve, the ketosis, and the impaired breakdown of liver glycogen suggest that the normal balance between insulin and its antagonists is upset. Hyperinsulinism cannot be the cause—though this would favour glycogen deposition in the liver—in view of the marked elevation of the blood sugar following the ingestion of glucose. Nor can adrenal insufficiency be held responsible, since the injection of adrenaline does not raise the blood sugar.

Experimental Work

Houssay, and Corkill, Marks, and White²² showed that rabbits deprived of their pituitaries were unduly sensitive to insulin, and suffered from hypoglycaemia. (These

are both prominent symptoms in von Gierke's disease.) This hypoglycaemia could not be overcome by the injection of adrenaline, and only with difficulty by the intravenous administration of glucose. What is more, the livers of these rabbits contained abundant glycogen. It would seem that in the absence of the pituitary the liver glycogen is not readily converted into glucose. Fluch, Greiner and Loewi,²³ in their experiments on frogs, showed that glycogen breakdown in the liver was impaired when the anterior lobe of the pituitary gland had been removed, but whether this is a direct or an indirect effect through the thyroid or adrenals has still to be worked out.

Still more recently Anselmino and Hoffmann²⁴ claim to have isolated from the anterior lobe of the pituitary what they term a "carbohydrate metabolism hormone." It has the property of diminishing the liver glycogen of rats a few hours after its injection; it can be found in the blood of fasting diabetics, but in the blood of normal people only after a carbohydrate-containing meal. The lack of this hormone might well cause glycogen to accumulate in the liver, and be responsible for the low blood sugar.

Clinical Considerations

Corroborative evidence of endocrine dysfunction is obtainable clinically. In von Gierke's¹ first case atrophic adrenals were found. It has been shown experimentally²² that ablation of the pituitary body leads to atrophic changes in the suprarenals (and thyroid). The case of Wagner and Parnas¹ began as a typical glycogen accumulation disease, but developed frank diabetes mellitus.

Several cases have been described as having an abnormal fat distribution, such as is encountered in disease of the pituitary gland. One of van Creveld's¹⁹ patients had a definite dystrophia adiposo-genitalis.

Hantschmann²⁵ describes a case of Simmond's disease which at necropsy showed atrophy limited to the anterior lobe of the pituitary body. The patient had the typical cachexia and wasting, and was found also to be hypersensitive to insulin and to be suffering from a chronic hypoglycaemia. Lyall and Innes²⁶ have recently described a severe case of diabetes where marked improvement of the diabetic condition took place concurrently with the development of a destructive lesion (cystic adenoma with beginning calcification) of the pituitary body. They consider that the patient's condition is clinically analogous to that of an experimental animal in which the intense diabetes caused by pancreatectomy is alleviated by hypophysectomy.

Conclusion

These experimental and clinical observations give strong support to the endocrine theory of origin of this condition. They suggest that the normal balance which obtains between the pituitary body and insulin is disturbed. To account for the amylorrhoea is more difficult. So far as we know neither the pituitary body nor its satellites (the suprarenal and the thyroid glands) are concerned with the intestinal digestion of starch, but it has been shown recently by E. C. Dodds and co-workers^{27, 28} that the posterior lobe of the pituitary body contains a substance capable of inducing a severe lesion of the acid-bearing area of the stomach—sometimes haemorrhagic, and sometimes of the nature of a chronic ulcer. Furthermore, the stomach of an animal which has received an injection of this pituitary extract will not yield hydrochloric acid, even after the injection of histamine. It is therefore not inconceivable that the pituitary may have some relation to the interaction of amylase and starch in the small intestine, if only from the hydrogen-ion concentration point of view.

Summary

1. A case of von Gierke's (glycogen accumulation) disease is described, and the presence of amylorrhoea, a new finding, is noted.

2. It is suggested that there is in this condition an inability on the part of the liver to convert animal starch (glycogen) into glucose, and an impaired digestion of vegetable starch in the intestine.

3. Possible mechanisms are discussed, and it is suggested that there is either (a) a disturbance of the pH in the immediate neighbourhood of the glycogen in the liver cells and in the immediate neighbourhood of the starch grains in the intestine, or (b) an endocrine disturbance, quite distinct from the more familiar ones in that the balance which normally exists between the carbohydrate metabolism hormone of the anterior lobe of the pituitary and insulin is upset.

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During 1935, the twelfth year of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, seventy applications for grants were received and twenty-five were approved, one of these being a continuation of an annual grant. Twelve of the new grants were awarded to scientists in countries other than the United States. Among the recipients were Professor P. Ellinger of London for the continuation of work on the physiology, pathology, and pharmacology of the kidney, and research on vitamin B deficiency. Dr. H. A. Krebs received a grant for experiments on the mechanism of ketogenesis and anti-ketogenesis. It is announced that grants will be given in the sciences closely related to medicine, without reference to special fields, the maximum size of the contribution being as a rule less than 500 dollars. Applications for grants must reach Dr. J. C. Aub, Collis P. Huntington Memorial Hospital, 695, Huntington Avenue, Boston, Massachusetts, before May 1st. There are no special forms of application, but letters asking for aid must state definitely the qualifications of the investigator, the character of the proposed research, the size of the grant requested, and the specific way in which the money will be expended. It is highly desirable to include letters of recommendation from the directors of laboratories or clinics in which the work is to be done.