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# Hyperglycaemia and Hypoglycaemia in Childhood

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Conditions of metabolism are similar in starvation, hypoglycaemia and diabetes. In the atrophic organism, the usual effect of hormones may be reversed. Fever or stress may reduce the blood sugar level in premature or marasmic infants instead of eliciting the usual hyperglyceamia. The newborn and the infant are not susceptible to ketosis, whereas — owing to the particularities of their metabolic processes — they show a high incidence of lactic acidosis.

Diabetes must not be regarded as a uniform, autosomally inheritable disease: it is rather a heterogeneous condition with an intricate genetic background. Postnatal transitory diabetes of the newborn and the problem of lactic acidosis associated with diabetes are discussed.

Starvation induces hypoglycaemia and acidosis. HETÉNYI [16] characterized diabetes as a form of starvation. Coma is, according to this concept, the natural outcome of diabetes, and it is a peculiar feature that the usual pattern of death from starvation is associated with symptoms due to the accumulation of secondarily developed ketone bodies and to the tissues being flooded by sugar.

Metabolic processes in diabetes and hypoglycaemia change in a similar manner. Neoglycogenesis is useful in diabetes because the organism is capable of utilizing glucose even if insulin is deficient, provided the blood sugar level is sufficiently high. Counterregulation in hypoglycaemia has likewise the purpose to raise the concentration of blood sugar to a level which ensures the glucose supply of the tissues.

It is comparatively easy to classify the various forms of hyperglycaemia; its permanent state is diabetes. The presence of latent diabetes or that of prediabetes is assumed if, owing to the hyperglycaemic condition, the patient occasionally develops a transitorily high blood sugar. This simplification of the hyperglycaemic states is possible because an insufficient insulin production by the beta cells is the immediate cause of the diabetic disturbance of metabolism. While there are exceptions to this rule, it certainly applies to childhood diabetes.

Owing to their reverse pathogenesis, hypoglycaemic conditions require a more complex classification. Fig. 1 represents an attempt to this end. Most forms of hypoglycaemia originate in infancy or childhood and many of them disappear in infancy or child-

hood, such as the neonatal McQuarrie-Zetterström hypoglycaemia [6, 23]. There are two major categories of hypoglycaemia according to whether or not they are accompanied by hyperinsulinism. The group of patients displaying hypoglycaemia with hyperinsulinism includes prediabetes. Conditions of hypoglycaemia and hyperglycaemia are correlated in so far as diabetes may be preceded by hypoglycaemia, a phenomenon only natural if it is assumed that the destruction of beta cells may be associated with their compensatory hypertrophy. Even temporary improvements following treatment in the initial phase of diabetes may be accompanied by spontaneous or reactive hypoglycaemia.

Hyperinsulinism may moreover give rise to hypoglycaemia in the newborn of a diabetic mother. The newborn has to adapt itself to a kind of carbohydrate metabolism different from that to which it had been adapted *in utero*. It is only natural that maternal endocrine conditions are decisively influencing the metabolism of the foetus. This influence is clearly demonstrated by the effect of the mother's parathyroid gland on foetal calcium and phosphorus metabolism. There are data to show that maternal hyperparathyroidism may induce neonatal hypoparathyroidism. The opposite, i.e., neonatal hyperparathyroidism as a consequence of maternal hypoparathyroidism, occurs more rarely; Gerlóczy and Farkas [12] were the first to describe a case of this kind. Data are lacking as regards the effect of maternal hypoglycaemia on foetal or

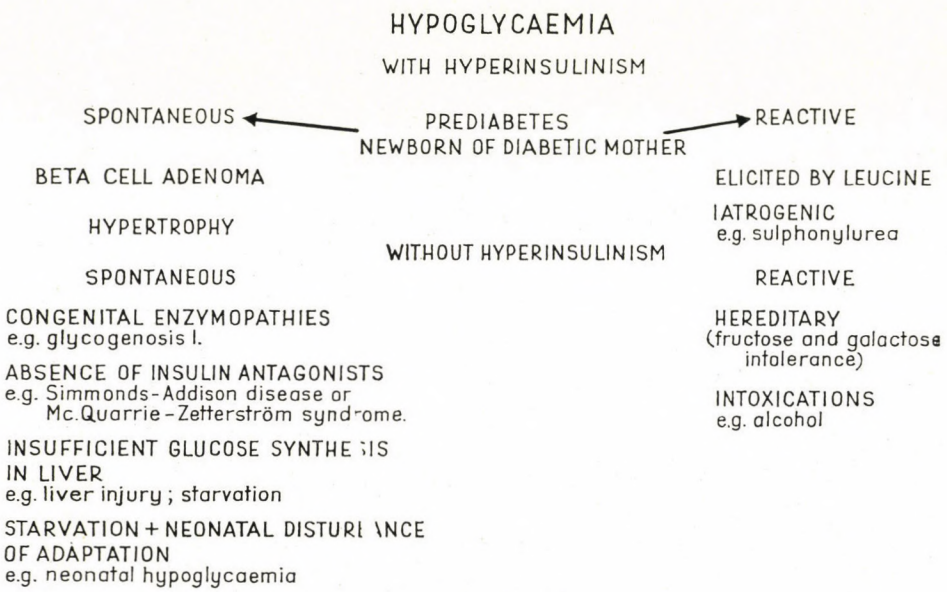


Fig. 1

neonatal metabolism. On the other hand, literature abounds in data concerning the effect of maternal diabetes and prediabetes on the newborn.

The method of treating hypoglycaemia, even those of unknown origin, is well-known. Hypoglycaemia of newborn and marasmic babies is of especial significance, for a reduction in the blood sugar level is often fatal. Kerpel-Fronius et al. [19, 20] emphasized the prognostic significance of hypoglycaemia in atrophic infants and showed that in such cases symptomatic hypoglycaemia carried a mortality rate exceeding 50%. They demonstrated that the endocrine condition of such infants was like that following hypophysectomy. These babies are unable to compensate the fall of the blood sugar level. The decrease of blood sugar is not accompanied by an elevated level of free fatty acid, a phenomenon due to the absence of fat depots, among others. The fact that glucagon depresses rather than elevates the blood sugar level, shows the exhaustion of reserves. We, too, recorded changes in the level of blood sugar under conditions of starvation. We have attempted to clarify how the blood sugar level changes in the starving organism treated with drugs or exposed to stress which increase the concentration of blood sugar under normal conditions. In marasmic rabbits fever decreased the blood sugar [4]. A notable decrease in the blood sugar level of young rabbits was obtained by stimulating their vegetative nerve centres with pentetrazole after 10 to 13 days fasting [5] (Fig. 2). It has been suggested that, while the need of glucose is increasing with the enhancement of metabolism, the liver, incapable of synthesizing glucose, cannot satisfy the requirement. The blood sugar level is low in cases of neonatal hypoglycaemia (which occurs mainly in prematures or in small for dates or, else, in those newborns whose life is endangered by the mother's toxaemia or some primary disease); this is presumably due to the

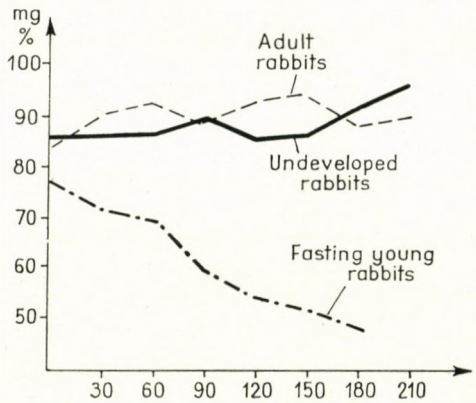


Fig. 2. Blood sugar curves in fasting animals under the effect of metrazole

fact that the liver does not produce the required amount of glucose, while the peripheral utilization of sugar is intensified. This hepatic failure may be due to a functional failure or a deficiency of enzyme synthesis.

If reactivity is normal, acidosis in hypoglycaemia is mostly caused by ketonaemia. It is by way of compensation that the ketonaemic patient develops acidosis. There are certain forms of hypoglycaemia in which the fall of the blood sugar level is associated with lactic acidosis. The cause of acidosis in sometimes known. In glycogenosis of type I, for instance, glycogen is not converted to glucose owing to the absence of glucose-6-phosphatase, whereas pyruvic acid and lactic acid production proceeds normally. The lactid acid level increases also in cases of hypoglycaemia induced by alcohol intoxication because large amounts of NADH are released at the degradation of alcohol to acetic acid, a phenomenon which stimulates the formation of lactic acid from pyruvic acid. In other cases, the mechanism of lactic acidosis is obscure. If follows from the foregoing that, if atrophic infants develop toxaemia, hypoglycaemia and not hyperglycaemia is to be expected and owing to an eventual disturbance of enzyme synthesis, such infants may be susceptible to lactic acidosis owing to the accumulation of pyruvic acid. It is likewise to the elevated level of lactic acid that the development of metabolic acidosis is attributed in cases of neonatal hypoglycaemia.

As mentioned above, metabolic processes tend to change in a similar manner in hypoglycaemia and hyperglycaemia; and according to recent investigations, in diabetes severe acidosis is frequently accompanied by an increased lactic acid concentration. High ketone and lactic acid levels are not simultaneously present in the blood. Susceptibility to ketosis is considerably less pronounced in newborns, infants and adults than in children [7]. Considering the significance of lactic acidosis, it seems important to examine the biochemical background and the underlying causes of the acidotic state. The condition is mostly induced by a deficiency of glucose or, in the case of insulin deficiency, an insufficient utilization of glucose. The cells cease to produce fat and this is followed by lipolysis (Fig. 3). Acetyl-CoA accumulates and changes into ketone bodies. Breakdown of glucose and amino acids is another source of acidosis. During starvation, after the exhaustion of the glycogen depots, the latter is still being formed from amino acids (Fig. 4). It is noteworthy in this condition that acetyl-CoA and oxalo-acetic acid are formed when sugar is broken down. It is from the union of these two compounds that citric acid originates which is then oxidized in the Krebs cycle. If, however, the organism imperatively requires sugar, oxalo-acetic acid changes back into phosphoenolpyruvate; the result will be that acetyl-CoA is not converted to citric acid so that the acetyl-CoA is transformed into

ketone bodies. The major part of ketone bodies thus originates from the breakdown of fat and a minor part from that of sugar and amino acids. It is evident from Fig. 4 that the formation of glucose from glycogen requires the presence of glucose-6-phosphatase. If no glucose is produced from glucose-6P, the concentration of pyruvic acid increases, a phenomenon favourable for the production of lactic acid. In glycogenosis of type I the accumulation of lactic acid is, as has already been noted, due to the lack of phosphatase. It is supposed that in certain cases of lactic acidosis, such as in those associated with liver injury or some enzymatic anomaly in the neonatal period, the accumulation of lactic acid is due to an insufficient production of phosphatase. The lactic acid level may be raised further by the accumulation of NADH in hypoxic states or in the cases of enhanced anaerobic glucose decomposition. Lactic acid is synthesized in the muscles, too, especially in hypoxia and in every

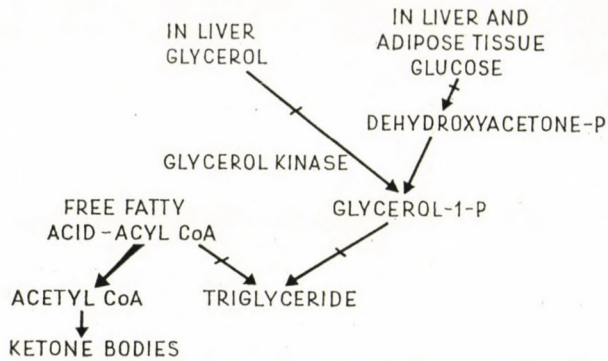


FIG. 3. Fat metabolism during fasting and in diabetes

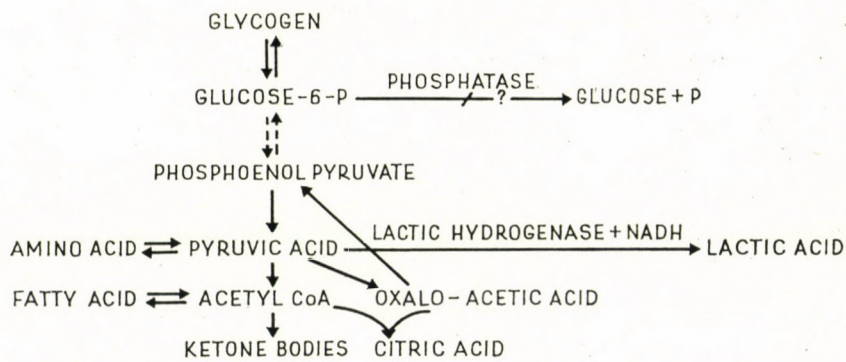


FIG. 4. Glycogen breakdown during fasting and in diabetes

condition associated with increased catecholaemia, thus on exposure to various stresses. All forms of acidosis, including lactic acidosis, which are not caused by the accumulation of ketone bodies inhibit the formation of these compounds. Lactic acidosis, acting against lipolysis, diminishes the production of acetyl-CoA. It follows that hypoglycaemia associated with neonatal circulatory disturbances and respiratory distress promotes the production of lactic acid. Newborn infants scarcely produce ketone bodies, while, in contrast to the case with marasmic babies, the mobilization of fatty acid begins in the very first hours of extrauterine life. This is in harmony with the fact that the level of growth hormone is high and that of insulin low in the blood of newborn infants. The utilization of fatty acid is presumably more intensive after birth than later. This may be due to the presence of the large amount of born fat tissue in the neonatal organism which oxidizes a correspondingly large amount of fatty acid [14, 15].

It has recently been found that lactic acid considerably increases the synthesis of glucagon in the pancreas. Although this is useful in cases of hypoglycaemia, the hyperglycaemic action of glucagon in the neonatal period is, as has been shown in newborn rats, weaker than expected [13]. The experiments of KERPEL-FRONIUS [19, 20] have shown that glucagon does not necessarily induce hyperglycaemia. We, too, observed that in some cases of obesity (and, presumably, of prediabetes) glucagon may give rise to a depression and nor to an elevation of the blood sugat level.

Drugs and hormones which usually raise the concentration of blood sugar may sometimes act in the opposite sense. Such a reversal may occur also with insulin. The mechanism of this phenomenon becomes clear if we study the interaction between this hormone and its antagonists. Insulin does not seem to gain access to the cells so that it acts on the cell membrane. It facilitates the entry of glucose and lipoids into the cell, blocks cellular lipolysis and promotes the synthesis of protein and fat. Whether processes taking place in the cells are anabolic or catabolic depends on the activity of cyclic AMP contained in the cell membrane [25, 26]. Insulin inhibits, contrainsular hormones stimulate the production of cyclic AMP. The metabolic role of the latter is represented in Fig. 5. It can be seen that insulin and the so-called lipolytic hormones produce opposite effects on 3'5' AMP while theophylline, by inhibiting the splitting of 3'5' AMP, increases its effects. Although insulin has an inhibitory effect on the production of cyclic AMP, the role played by 3'5' AMP in the secretion of insulin is nevertheless significant. Again, glucagon stimulates the production of insulin. It is, thus, a peculiarity of hormones acting in opposite directions that they stimulate each other's formation. It is therefore easy to understand that any metabolic disturbance may turn into the opposite of the usual effect on blood sugar of hor-

mones and drugs. Fever or stress induce instead of the usual hyperglycaemia a fall of the blood sugar level in newborn or marasmic infants, a phenomenon of significance in connection with the development of hypoglycaemia. It has been mentioned

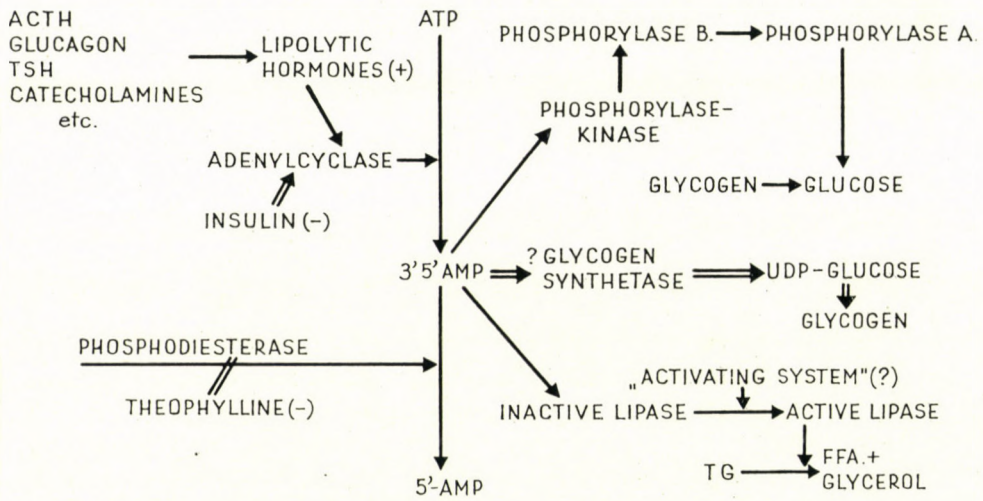


FIG. 5

that the susceptibility to ketosis is negligible in the neonatal period and in infancy, whereas, owing to the peculiarity of the metabolic processes and the nature of the pathologic conditions, lactic acidosis is a frequent occurrence.

It has been said that it is easy to classify the varieties of hyperglycaemia. Generally speaking, any kind of hyperglycaemia may be classified as diabetes mellitus. On the other hand, diabetes mellitus should not be regarded as the primary disease of a given organ since there may be a number of pathogenic factors in its background. There are still sevreal unelucidated problems concerning its origin. There is general agreement that the disease is inherited recessively. Observation of adult diabetics has, however, shown that a single gene suffices for the appearance of the disease; certain investigators accordingly suggest that the inheritance may be both recessive and dominant. Most data agree also in that childhood diabetes is the result of recessive inheritance. Exogenous factors, the manner of life, etc., are known to be decisive for the manifestation of the condition. For instance, the proportion of diabetes is smaller among the country population than in urban areas. While diabetes is rare among negroes in Africa, its frequency among the negro population of the USA does not essentially differ from the general average. Diabetes in Ireland is less

frequent than among Americans of Irish descent. While such differences do exist in respect of adults, they do not apply to children in whom the manifestation of diabetes is but slightly influenced by outside factors. The diabetic disturbance of metabolism is due to an insufficient production of insulin by the beta cells; since the progress of the disease is rapid in childhood, the beta cells are destroyed at a comparatively quick pace, the result being a so-called total diabetes. It was, therefore, reasonable to assume that diabetes was caused by a congenital dysfunction of the beta cells. Although this theory is still acceptable in respect of a number of cases, recent investigations have shown that, owing to congenital or acquired immunological factors, the otherwise sufficient amount of insulin may be bound and become ineffective; the immune substances may reach the foetus via the placenta.

Disturbances of insulin formation or its decomposition, too, may lead to hyperglycaemia (e.g., an increase of insulinase activity in the liver), so that diabetes might arise from congenital enzymatic defects. Diabetes may result further from the reduced production of substances which stimulate insulin secretion, such as gastrin, secretion and glucagon. Besides, it has long been known that an increased synthesis of certain contrainsular hormones (growth hormone, ACTH, glucocorticoids), too, may induce diabetes. It is thus clear that diabetes has a varied background.

Paediatricians [27] observed long ago that diabetes mellitus was frequently associated with various congenital anomalies. Geneticists contributed further data in this respect: FORBES and ENGEL [10], for instance, pointed out that gonadal dysgenesis and diabetes were frequently associated. That irregularities pointing to diabetic disorders of the metabolism frequently occurred in connection with gonadal dysgenesis was subsequently observed by several authors who found moreover that the glucose and insulin tolerance curves were often abnormal even in cases in which the presence of diabetes was not demonstrable. Identical observations were made in connection with Klinefelter's syndrome. Diabetes is further a frequent concomitant of the Prader–Willi syndrome [24].

Diabetes mellitus associated with a number of congenital anomalies occurred with a certain frequency in our material; among 180 diabetic patients there was one case of Down's syndrome, one of oligophrenia with low stature and chromosomal aneuplody, there were two cases of hypotension with mental retardation, three cases of congenital cardiac defect and five cases of oligophrenia. Thus, their incidence was considerably higher than in the general population.

Although the incidence of oligophrenia was relatively high in our material, many diabetic children show a supernormal I. Q. The number of diabetics who have been followed since childhood include several doctors and engineers. It may be due to the

frequency of extremes that the number of average types is lower among diabetic children. All these observations tend to show that diabetes is not an autosomally inherited uniform entity but a heterogeneous condition with an intricate genetic background. This is why the question has been raised [22] whether diabetes should be classified as a disease or a syndrome. According to present knowledge, not less than 16 kinds of genetic anomaly may be associated with diabetes, thus the genetic background is far from being uniform. Symptoms have been registered in connection with diabetes that had apparently nothing to do with metabolic disturbances.

Vascular damage is believed to be an extremely grave, even fatal, sequel of diabetes. Since, however, characteristic vascular changes are frequently seen in patients with prediabetes and also in the relatives of diabetic patients, even specific vascular disorders are not regarded as resulting from a diabetic disturbance of metabolism but as a characteristic peculiarity of the diabetic condition.

Once present, the progress of vascular lesions is influenced by metabolic factors. Degenerative processes of the vessels being rare in childhood, it seemed justified to study their frequency in diabetic children. Ophthalmoscopically verified retinopathy has been recorded as from the 9th year of age. Similar observations have been made in our patients. Examination of the eyeground by means of fluorescein angiography revealed still more interesting details, viz. ophthalmoscopically not perceptible initial changes, fine solitary or grouped microaneurysms, the presence of which was independent of the duration of diabetes. Such lesions appeared from the 8th year of age and were not influenced by the nature of the treatment. It is clear that the early signs of diabetic angiopathy are independent of metabolic processes and should, therefore, be regarded as a symptom of the diabetes syndrome [3].

Neonatal diabetes has amply been investigated in the last ten years. In the case of a benign metabolic disturbance the symptoms take a few weeks or less frequently 12 to 18 months to disappear. Such benign conditions usually start in newborn infants with a low birth weight. They are not associated with any infection. Dehydration is a characteristic feature. Therapy in such cases is more or less the same as in cases of diabetic coma. As a rule, disturbances of this kind do not develop into permanent diabetes. It has been suggested that the condition is induced by some central regulatory disturbances or sometimes by adrenal hyperactivity. None of these theories has convincingly been proved. It is rather a delayed maturation of the beta cells that transitory diabetes is attributed to. It develops in the first month of extrauterine life. In spite of the high blood sugar level, no acetonuria is demonstrable. CORNBLATH and SCHWARTZ [8] selected 15 cases from the literature, and it was only in a single instance that the urine was acetone positive. At the same time, acidosis may develop. What has

been noted above in respect of neonatal hypoglycaemia applies thus to neonatal hyperglycaemia as well. The disposition to produce acetone is very slight and, considering that hyperglycaemia may give rise to acidosis, it seems justified to suppose that in these cases the acidosis results from

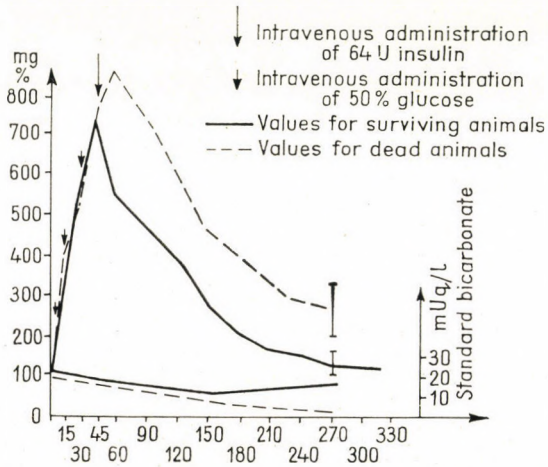


FIG. 6. Blood sugar and standard bicarbonate after glucose + insulin loading

the increased concentration of lactic acid.

Diabetes in infancy is rare but, when present, it carries a high mortality rate. We had recently a three-month-old baby with diabetic coma whose acidosis was partly due to ketosis and partly to lactic acid accumulation. The blood sugar showed variations during the 6-month period of observation and rose steeply from time to time, but repeated examinations failed to reveal acetonuria.

Acidosis caused solely by the accumulation of lactic acid is rare in connection with coma in older children. We have observed two such cases. Both children had received an impermissibly large amount of sugar, the one orally, the other intravenously. The resulting high blood sugar was accompanied by lactic acidosis and a low blood ketone level. Lactic acidosis is usually observed after the efficient treatment of coma with insulin: the level of ketone bodies decreases, that of lactic acid increases in such cases. Acidosis of this mixed kind has often been observed in our material and could be reproduced in animals. Administrations of sugar or sugar and insulin induced lactic acidosis, a phenomenon in which the antiketogenic action of glucose may have been involved.

If we induce hyperglycaemia in rabbits by the intravenous administration of 50% glucose and treat them with insulin, those animals will develop lethal acidosis in which the blood

sugar shows a paradoxically high value owing to insulin resistance (Fig. 6). The paradoxical increase in blood sugar after the administration of insulin [2] goes hand in hand with the development of lactic acidosis. The mechanism of the process is fairly clear; the anaerobic oxidation of glucose is enhanced if the level of blood sugar is high. Values exceeding 800 mg per 100 ml mean a hyperosmolarity which facilitates the development of circulatory disturbances. The paradoxical elevation of the blood sugar level points at the same time to a contrainsular action which predisposes to lactic acidosis. It so happens that the level of lactic acid starts rising before the patient goes into a state of shock and assumes a fatally severe form when the shock has become fully developed.

Coma in the diabetic patient represents a stress the consequences of which are felt for years. Statistics make it evident that the more frequent the comatose conditions in the course of treatment the earlier the development of complications and the more serious they are. It is well-known that the somatic and psychic development of adequately treated diabetics is satisfactory and that they may become valuable members of the community.

Diabetes may manifest itself with various symptoms before it is detected so that the course of the disease is variable in children. Certain cases are difficult to manage. In 10% of the cases the course of the disease is so capricious as to make home care and treatment impossible. Social adjustment of the child, its position in society, the choice of profession, etc., mean serious problems even in comparatively well manageable cases. It is up to the society to solve the practical problems of this kind, and a close and harmonious cooperation of paediatricians, parents and teacher is necessary if we want to improve the prognosis of the disease.

## References


1. Arey, S. L.: Transient diabetes in infancy. Pediatrics **11,** 140 (1853).
2. Barta, L.: Über die Bedeutung der Milchsäure-Azidose bei diabetischem Koma im Kindesalter. Acta paediat. Acad. Sci. hung. **11,** 285 (1970).
3. Barta, L., Brooser, G., Molnár, M.: Diagnostic value of retinal fluorescence angiography in juvenile diabetes. Acta paediat. Acad. Sci. hung. **12,** (1971).
4. Barta, L., Kocsis, M.: Über den Zuckerstoffwechsel des atrophischen Organismus. Ann. Paediat. (Basel) **187,** 461 (1956).
5. Barta, L., Vedres, M.: A vércukorszint változásai éhezéses állapotban metrazol hatására. Gyermekgyógyászat **13,** 316 (1962).
6. Broberger, O., Jungner, I., Zetterström, R.: Studies in spontaneous hypoglycemia in childhood. J. Pediat. **55,** 713 (1559).
7. Brock, J., Knauer, H., Rudder, B., Becker, B., Klinke, R.: Biologische Daten für den Kinderarzt, III. Springer, Berlin 1939.
8. Cornblath, M., Schwartz, R.: Disorders of carbohydrate metabolism in infancy. Saunders, Philadelphia 1966.
9. Engleson, G., Zetterqvist, P.: Congenital diabetes mellitus and neonatal pseudodiabetes mellitus. Arch. Dis. Childh. **32,** 193 (1957).
10. Forbes, A. P., Engel, B.: The high incidence of diabetes mellitus in 41 patients with gonadal dysgenesis, and their close relatives. Metabolism **12,** 428 (1963).
11. Gegesi Kiss, P., Barta, L.: Diabetes mellitus im Kindesalter. Akadémiai Kiadó, Budapest 1967.

12. Gerlóczy, F., Farkas, K.: The hyperparathyroidism of a new-born descending from a mother with chronic hypoparathyroidism. Acta med. Acad. Sci. hung. **4,** 73 (1953).
13. Girard, J., Bal, D., Assan, R.: Rat plasma glucagon during the perinatal period. European Diabetes Association 7th Annual Meeting, Southampton 1971.
14. Heim, T., Kellermayer, M.: Effect of starvation on brown adipose tissue in the new-born rabbit. Acta physiol. Acad. Sci. hung. **30,** 107 (1966).
15. Heim, T., Kellermayer, L., Dani, M.: Thermal conditions and the mobilization of lipids from brown and white adipose tissue in the human neonate. Acta paediat. Acad. Sci. hung. **9,** 109 (1968).
16. Hetényi, G.: Az anyagcsere-betegségek kór- és gyógytana. MOKT, Budapest 1933.
17. Hetényi, G.: Arteriosclerose. In: R. Boller (Herausg.) Diabetes Mellitus. Urban und Schwarzenberg, Wien 1950.
18. Hutchinson, J. H., Keay, M. M.: Congenital temporary diabetes mellitus. Brit. med. J. **2,** 436 (1962).
19. Kerpel-Fronius, E., Jáni, L., Fekete, M.: Disaccharide malabsorption in different types of malnutrition. Ann. Paediat. (Basel) **206,** 245 (1966).
20. Kerpel-Fronius, E.: Volume and composition of the body fluid compartments im severe infantile malnutrition. J. Pediat. **56,** 826 (1960).
21. Labhart, A.: Klinik der inneren Sekretion. Springer, Berlin—Heidelberg—New York 1971.
22. Lancet (Editorial): Diabetes mellitus: Disease or syndrome? **1,** 383 (1971).
23. McQuarrie, I.: Idiopathic spontaneously occurring hypoglycemia in infants. Amer. J. Dis. Child. **87,** 399 (1954).
24. Prader, A., Labhart, A., Willi, H.: Ein Syndrom von Adiposität, Kryptorchismus und Oligophrenie nach myatonieartigem Zustand im Neugeborenenalter. Schweiz. med. Wschr. **86,**1269, (1956).
25. Sutherland, E. W., Rall, T. W.: Fractionation and characterisation of a cyclic adenine ribonucleotide by tissue particles. J. biol. Chem. **232,** 1077 (1958).
26. Sutherland, E. W., Robinson, G. A.: Metabolic effects of catecholamines. Pharmacol. Rev. **18,** 144 (1966).
27. Wagner, R., White, P., Bogan, J. K.: Diabetic dwarfism. Amer. J. Dis. Child. **68,** 667 (1942).

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