Round Table Discussion

METABOLIC DISEASES IN CHILDREN

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(Reading of Chairman Najjar’s paper.)

Chairman Najjar: I have indicated to you that the alpha cells of the pancreas excrete the hyperglycemic factor. The practical value of this finding can only be measured by its possible bearing on the understanding and treatment of aberrations of carbohydrate metabolism. Dr. Irvine McQuarrrie has lately found cases of hypoglycemia that showed absence of these cells. This finding is of great significance in future therapy of this condition. What may have taken years to recognize is now an accomplished fact. This we owe to the keen efforts and observations of Dr. McQuarrrie who will now address us.

Dr. Irvine McQuarrrie, Minneapolis: Dr. Najjar has covered the fundamental aspects of the interrelationships between hormones and enzymes involved in carbohydrate metabolism so thoroughly that I shall not need to comment on that phase of the subject in my discussion of the hypoglycemosis (hypoglycemic state), but will lean heavily upon our clinical and pathologic observations.

Spontaneously occurring, persistent hypoglycemia of severe grade with such manifestations as repeated convulsions and attacks of coma, which may be followed by irreversible damage to the central nervous system if inadequately treated, is, fortunately, a comparatively uncommon disorder. On the other hand, milder forms of the condition, characterized by such symptoms as a vague sensation of hunger or gauntness, a feeling of faintness or weakness, cold sweats and other vasomotor reactions, tremulousness, dizziness, mental confusion, drowsiness and occasional convulsions, occur with far greater frequency than most physicians appreciate. It has been estimated by several authorities on the subject that the total number of persons in the United States who are afflicted with the syndrome is almost as great as the number known to suffer from diabetes mellitus.

The complexity of the problems of etiology, classification, diagnosis and treatment of spontaneous hypoglycemia is illustrated by the schema presented in the first slide. The concept of the blood sugar concentration being dependent upon a balance between the functional activity of the insulin-producing system on the one hand and the combined activities of a series of hyperglycemia or anti-insulin factors on the other is expressed through the symbol of an old-fashioned steelyard provided with a modern pointer and scale. According to this concept, every case of spontaneous hypoglycemia is due to either absolute or relative hyperinsulinism.

The expression, “true, or absolute hyperinsulinism,” obviously implies therapeutic insulin overdosage or overproduction of insulin by the beta cells of the pancreas. While it is conceivable that normally appearing isular beta cells might produce excessive amounts of insulin at times in response to nervous or other extrapancreatic stimuli, the evidence that this is an important cause of spontaneous hypoglycemia in any but the mildest cases is not entirely convincing. Tumors (adenoma and carcinoma) and hyperplasia, involving the beta cells of the pancreatic islands, constitute the only satisfactorily demonstrated pathologic lesions associated with absolute hyperinsulinism. Successful surgical excision of a benign islet tumor results in complete cure of the hypoglycemosis. Such tumors are extremely rare in children. Subtotal pancreatectomy in cases showing islet hyperplasia is frequently highly beneficial, at least temporarily.

Alloxan used by Talbot and coworkers as a last resort in one severe case of hyperinsulinism appeared to give satisfactory results. Because of its marked hepatotoxic and nephrotoxic action, this agent should obviously be used with extreme care if used at all.

The term “relative hyperinsulinism” refers to the state in which hypoglycemia results from


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underactivity of one or more of the nervous, hormonal, nutritional or other antagonistic factors lined up in our schema on the side of the balance opposite that occupied by the symbolic pancreas. Hypocorticoadrenalism (Addison’s disease), anterior pituitary deficiency (Simmonds’ disease and certain cases of pituitary dwarfism), extensive liver disease (necrosis, atrophy, acute hepatitis, cirrhosis and von Gierke’s glycogen storage disease) are the most commonly recognized disease entities causing relative hyperinsulinism. In all these clinical conditions the hypoglycemia is characterized by its appearance almost exclusively at times most remote from meals, indicating a deficiency in the glycogen stores of the liver or a deficiency in the mechanism for breakdown of glycogen to glucose (glycogenolysis), as in von Gierke’s disease. The net clinical significance of deficiencies in the cellular activity of the thyroid, posterior pituitary, adrenal medulla, islets of Langerhans (alpha cells) and ovaries and of disturbances in the functions of the sympathetic and parasympathetic nuclei in the hypothalamus, as regards the production of hypoglycemia, cannot be accurately appraised at the present time. Perhaps future investigations on these aspects of the problem will shed new light on the pathogenesis of so-called idiopathic hypoglycemia, which constitutes the largest single group of hypoglycemia children in our experience.

As regards treatment of the etiologically different types of spontaneous hypoglycemia, nothing further needs to be said concerning true hyperinsulinism. Obviously, for those patients who suffer from adrenocortical insufficiency or pituitary insufficiency, specific replacement therapy and avoidance of fasting are indicated. The most important feature of the therapy for hypoglycemia due to the various forms of liver disease already referred to is that which is directed to the primary disease itself. In the milder forms of so-called functional hypoglycemia, the etiology of which is more or less obscure, the most satisfactory form of treatment is that involving the use of the high-protein, comparatively low-carbohydrate diet recommended by Conn.

Shortly after it was announced by Corey and Britton and by Long in 1939 that adrenal cortical extract in excessive dosage exerts a diabetogenic effect in normal animals, we attempted to exploit the discovery by administering comparatively large doses of commercially available extracts to young children suffering from severe spontaneous hypoglycemia of non-Addisonian type. While the results in a few instances were mildly encouraging, they were not sufficiently definitive to justify the expense entailed in routine use of the extract.

On the basis of the well-known observation by Young and by others, that continued administration of crude extracts of the anterior lobe of the pituitary gland produces glycosuria and hyperglycemia (diabetogenic effect) in normal experimental animals, we treated a young hypoglycemic pituitary dwarf with large doses of one of the then available commercial extracts of this gland (polyansyn®, Armour) in 1940. The patient had had generalized convulsions on several occasions while his fasting blood sugar was in the neighborhood of 20 mg. %. Morning convulsions ceased to occur and his fasting blood sugar subsequently was found to be within normal range. A recent check on the patient’s progress revealed that convulsions have never recurred.

When adrenocorticotropic hormone (acthar®) was found by Brown (1943) and by Conn (1948) to induce hyperglycemia and glycosuria in normal men, it became apparent to us that its effects on spontaneous hypoglycemia should be studied.

Metabolic data on 12 non-Addisonian hypoglycemia patients included in our study of the problem indicate that their responses to ACTH administration are similar in type to those reported for normal adult subjects. Severe hypoglycemia and attendant symptoms were completely abolished during the period of intensive hormone administration and usually for a few days after its withdrawal. The sharp fall and the abnormally prolonged, low level of blood sugar in the glucose-tolerance curve, which represented the characteristic response of each of the patients during the control period, were found to be absent during the period of ACTH administration, the curve becoming essentially normal. The eosinophil cells of the blood fell precipitantly from the normal range (between 100 and 350 cmm.) to between 0 and 10 cmm., within 4 hours after ACTH was first administered and remained at this low level so long as the hormone was given at 6 hour intervals.

As Dr. Najjar has indicated, it has been demonstrated by previous workers in experimental animals that the alpha cells of the islets of Langerhans exert an anti-insulin or hyperglycemic (glyco- genolytic) effect. We have recently made metabolic and histologic studies on 2 patients suffering from spontaneous hypoglycemia (brother and sister) in whom absence of pancreatic alpha cells appears to be the most likely etiologic factor. Special biochemical tests for dysfunction of the adrenal cortex, the adrenohypophysis and the liver were negative. No evidence of adenoma or hyperplasia of the beta cells of the pancreatic islets could be found in these two patients when subtotal pancreatectomy was performed. However, examination of sections of the pancreas stained with
Gomori's special stain unexpectedly revealed the total or almost total absence of alpha cells. That the patients showing these unusual characteristics represented a heretofore unrecognized endocrinologic entity is suggested by the familial occurrence of the syndrome and the initial appearance of symptoms during the first months of life. Adrenocorticotrophic hormone was found to be highly effective in control of the hypoglycemia. In fact, this new hormone appeared to be as effective for the control of all cases of non-Addisonian hypoglycemia as insulin is for the control of diabetes mellitus. Our most severe case, the younger of the 2 with absence of alpha cells, lost her tendency to spontaneous attacks of hyperglycemia after one year of ACTH therapy.

Fasting hypoglycemia and morning convulsions were prevented temporarily by ACTH therapy in one young patient with glycogen storage disease. The glycogenolytic substance derived from the pancreas did not induce hyperglycemia in this patient with von Gierke's disease.

Dr. Philip Rosenblum, Chicago: Would growth hormone be indicated for hypoglycemia in view of what Dr. Najjar has said?

Dr. McQuarrie: It inhibits carbohydrate metabolism so I would be reluctant to try it for fear it might do some harm.

Chairman Najjar: Growth hormone seems to depress glucose uptake so that one might get an overall effect of combatting hypoglycemia. However, since the effect of the hormone is not limited to carbohydrate metabolism, I would hesitate to use it as a therapeutic measure.

Dr. Francis W. Heltrick, Manchester, Conn.: Has anyone had experience with ACTH in the glycogen storage disease of muscle, distinct from that of the liver type?

Chairman Najjar: I do not know of any published work on the effect of ACTH on liver glycogen as contrasted to its effect on muscle glycogen disease.

Dr. Holt has been interested in glycogen disease for quite some time. I am sure we will all welcome Dr. Holt's comments on this subject.

HEPATIC FORM OF GLYCOGEN DISEASE (VON GIERKE'S DISEASE)

Dr. L. Emmett Holt, Jr., New York City: My remarks will be confined to the hepatic form of glycogen disease (von Gierke's disease), the only one in which I have had any experience. A few years ago Dr. Edward Bridge and I reported upon this disease. We made some clinical observations, noting among other things a tendency to obesity and a favorable response to indirect carbohydrate therapy (e.g., extra protein therapy). We also attempted to throw light on the nature of the glycogenolytic defect. I shall now report some experiences and further observations made in the interim which have in part confirmed and in part changed the points of view we held at that time.

I am inclined to think that Dr. Bridge and I were unduly rigid in demanding that the liver should contain 10% or more glycogen to establish the diagnosis of von Gierke's disease. I have since seen unquestionable cases in which analysis of biopsy specimens gave a lower figure. In the past glycogen disease has been regarded as an all-or-none affair; different grades of severity were not appreciated. There is, however, suggestive evidence that differences in severity exist. This evidence is partly clinical, partly chemical and partly histologic. Hypoglycemia is much more of a problem in some patients than others, and the same may be said of ketosis. The glycogen content of the liver may vary at least between the limits of 6% and 15%. In typical cases the microscopic appearance of the liver cells is characteristic—they are large "plant-like" cells—3 to 4 times the diameter of a normal liver cell, with a centrally placed nucleus and small cytoplasmic granules filled with glycogen. In appearance they resemble early embryonic hepatic cells and all the liver cells are so affected. My colleague, Dr. William Von Glahn, has called my attention to the existence of livers in which the typical appearance of von Gierke's disease is present in certain areas of the liver only, those elsewhere appearing quite normal. It is of interest in this connection that in the cardiac form of von Gierke's disease the large vacuolated embryonic type of cell commonly affects the entire heart. However, there are encountered hearts in which such changes are found only in localized areas. These cases are usually diagnosed as rhabdomyoma. Thus it is possible that both in the hepatic and cardiac forms of glycogen disease incomplete forms may exist.

Acetonuria is commonly thought to be an invariable and striking characteristic of hepatic glycogen disease. We were troubled at not finding this symptom in an otherwise typical case until the report of Van Creveld came to our attention, pointing out that acetonemia may exist without acetonuria. The suggestion has been made that when the glycogen disease affects the kidney as well as the liver, this situation may prevail. Studies of kidney function in renal glycogenosis are needed to confirm this.

Although hepatic glycogen disease is commonly thought to be a disorder of carbohydrate metabolism alone, it has been clear for some time that there is, during infancy at least, a concomitant disorder
of fat metabolism. The literature contains a number of reports of lipemia in these cases and Dr. Bridge and I, in one of our patients studied in Baltimore, observed the disappearance of this phenomenon between the age of 2 and 6 years. A second instance of such disappearance has since come to my attention. In keeping with the observations on early lipemia are analyses of the liver itself made at this period in the disease which have shown abnormal accumulations of fat together with glycogen; such findings have not been reported in older subjects.

As Dr. Najjar has pointed out, the nature of the glycogenolytic defect in this disease is still obscure—it may be that the glycogen itself is abnormal in structure or it may be that the enzyme system is faulty. Since most enzyme systems are reversible it is difficult to explain the coexistence of defective glycogenolysis with normal glycogenesis. There is, however, evidence that in one step of the process a different enzyme is concerned in the synthetic and the lytic process: the formation of glucose 6-phosphate from glucose is performed by the enzyme phosphokinase, whereas the degradation of glucose 6-phosphate to glucose is performed by glucose 6-phosphatase. This unusual relationship suggested to us that glucose 6-phosphatase might be the deficient factor in glycogen disease, since such a deficit would permit normal glycogenesis but defective glycogenolysis. Through the kindness of Dr. Spurtes in Dr. Ochoa’s department measurements of glucose 6-phosphatase were made on a specimen of liver removed at biopsy from one of our patients. The quantity of this enzyme was found to be low as compared with a normal liver. We do not, however, feel justified in drawing the conclusion that glucose 6-phosphatase is defective in this disease since the size of the liver must also be taken into account. Even though the enzyme was low in terms of a unit of liver weight, the quantity present in the liver as a whole did not appear to be reduced.

I shall close by mentioning some recent clinical experiences with von Gierke’s disease—some pleasant and some the contrary. On the positive side, we have had further clinical experience with an additional late evening meal, high in protein and can confirm the observation that under these conditions normal growth is resumed, the additional protein serving to make up for the protein which in this disease is diverted from growth needs to meet the needs of carbohydrate metabolism. There is also now available from several sources information indicating that some tendency to recovery from the carbohydrate metabolic defect occurs with adolescence, and it may be that complete recovery eventually occurs.

On the unpleasant side I should like to record two experiences. In one instance in which my advice was sought as to whether a further pregnancy should be undertaken in a family whose first child had died of glycogen disease, I made the error of belittling the possibility of its occurrence in siblings and was properly embarrassed when the second child exhibited the disease. When one considers the reports of glycogen disease in the literature, most have been isolated instances and only a few have been in siblings. However, when one considers the reports in which information on siblings was available, the familial incidence is impressive.

My second unpleasant experience was in the case of a child of 11 months with what appeared to be a minor upper respiratory infection who was fasted 16 hours to make observations on the blood sugar curve. The patient went into collapse, developed hyperpnea, was found to be acidic and hypoglycemic and despite vigorous administration of intravenous glucose, the hypoglycemia was difficult to control and a fatal termination occurred within a few hours. A second patient, in which the sequence of events was almost identical, I saw with Dr. Murray Bass, who has knowledge of several other like ones. The explanation for these untoward episodes is not altogether clear. The acidosis was not a ketone body acidosis, judged by the absence of ketonuria, but this does not exclude the possibility of ketonemia without ketonuria. Accumulation of lactic acid has been noted by H. H. Mason under such circumstances and we may have been dealing with a lactic acidosis. It is difficult to escape the conclusion that some defect of carbohydrate utilization is coupled with the defect of glycogenolysis. Only thus can one account for the difficulty in sustaining the blood glucose level. Resistant hypoglycemic states have been observed in other conditions—particularly in terminal diarrheas. Whatever the explanation these experiences have made us extremely cautious in carrying out any procedure that involves even very temporary withholding of food.

Dr. Harry T. Nagel, Maywood, Ill.: Has ACTH been tried in the therapy of glycogen storage disease?

Dr. Holt: We treated one of the cases in Baltimore with cortisone which was then known as compound E. There was only a small amount available, enough to treat a patient for one day. This was inadequate treatment for it failed to accomplish anything.

Dr. Samuel S. Glick, Baltimore: Have you had any experience with cases of glycogen disease involving the heart?

Dr. Holt: No.
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Dr. D. Throston, Glendale, Mo.: In what way do salicylates interfere in carbohydrate metabolism? I mean salicylate poisoning where you get hypoglycemia. The British have reported the use of salicylates given in large doses in a syndrome that is characteristic of the one due to excess cortisone.

Chairman Najjar: The effect in salicylate poisoning may well be due to excessive utilization of glucose. The increase in metabolism following high doses of salicylate may be the result of increased tissue respiration. The effect may be similar to that exerted by dinitrophenol. This substance increases the metabolic rate apparently by dissociating two well coordinated processes in metabolism, i.e., oxidation and phosphorylation. Thyroxine seems to act in such a manner. If salicylates have a similar effect, then the absorption of glucose will be interfered with and what is absorbed will be quickly oxidized, eventually producing hypoglycemia.

Dr. H. B. Rosbber, Detroit: Dr. Holt, do these defects right themselves after the age of puberty?

Dr. Holt: Yes, as far as I know.

Chairman Najjar: In connection with this question I would like to stress the possible multiplicity of defects in this disease. As I mentioned earlier, the glycogen in one case tested by Dr. G. Cori was abnormal. That case had cirrhotic changes in the liver. On the other hand, similar cases were also studied and showed a normal type of glycogen. This then is definitely not the only defect one might encounter in glycogen disease. When an organ like the liver can synthesize glycogen, it necessarily means that all the enzymes needed for synthesis are present. With the exception of the first enzyme, hexokinase, all the others are reversible down to the glucose-6-phosphatase step. This step is the most logical one to incriminate, in that the enzyme would be absent in glycogen disease of the liver. If that is true, this type of defect can apply only to glycogen disease of the liver, since normal muscle has no such enzyme and therefore cannot produce glucose from its glycogen stores. Glycogen disease of muscle would be caused by some other type of defect.

Dr. Nelson Neu'mark, Springfield, Mass.: How often do you do a liver biopsy or muscle biopsy for diagnosis?

Chairman Najjar: If there is a large liver with symptoms of hypoglycemia, one is fully justified, I believe, in suspecting glycogen disease and for verification a liver biopsy would be indicated. Regarding muscle biopsy, the problem is a little different. Cases with glycogen disease of muscle alone show little or no demonstrable disturbance in carbohydrate metabolism. The only clue they offer is enlargement of the heart and cardiac failure. Under these circumstances, when no common disease of the heart is suggested by the course of the illness, then one is justified in obtaining a piece of skeletal muscle for study.

Dr. Carl Zelson, New York City: Did you find an increase in urinary amylase with a decrease in blood amylase?

Dr. Holt: Amylase was not studied.

Dr. Carl Zelson, New York City: In my case we had a definite decrease in blood amylase with a marked increase in urinary amylase.

Dr. Holt: We tried amylase in vitro; the glycogen was split down. We tried treating a child with amylase without any effect at all.

Dr. Hyman Alford, Newton, Mass.: Are there any characteristic ECG changes?

Dr. Holt: There have been ECG changes reported but I wouldn't say they are characteristic.

Chairman Najjar: Before proceeding with another aspect of this problem which Dr. Lytt Gardner will discuss, I would like to comment on the question that Dr. Holt raised regarding the irreversible hypoglycemia observed by him and leading to death. It is fortunate that such cases are in the minority. Most cases of glycogen disease do not show such severe hypoglycemia. The irreversible damage may well be due to the fact that brain tissue that derives its nutrition mainly from glucose cannot under certain circumstances withstand prolonged hypoglycemia. Either that, or that the real damage is done when there is loss of potassium from the brain cell due to poor availability of glucose. It has been demonstrated that potassium moves out of the cells when glucose is withheld from brain tissue and moves back in again when glucose is furnished.

We will now hear from Dr. Lytt Gardner, who will discuss some hormonal influences on carbohydrate metabolism.

EXOGENOUS HYPERADRENOCORTICISM

Dr. Lytt I. Gardner, Baltimore: It seems appropriate at this time to review some of the metabolic effects of exogenous adrenocortical hormones on protein, carbohydrate, fat and electrolyte metabolism. These effects bear directly on the function of cellular enzymes, since enzymes are proteins which participate intimately in intermediary organic metabolism, and which require a specific ionic environment.
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Such considerations are also essential to a proper understanding of the toxic effects which may result from the administration of ACTH or cortisone-like steroids.

Whereas endogenous hyperadrenocorticism of the Cushing's syndrome type is a rare disease in children, the last 2 years have seen exogenous hyperadrenocorticism due to ACTH or cortisone become a common pediatric condition. Furthermore, new adrenal steroids are on clinical trial, and it is likely that the pediatrician will soon have to cope with them. Hydrocortisone (compound F; 17-hydroxycorticosterone) has recently been administered orally to adult arthritic patients by Ward, Slocumb, Polley, Lowman and Hench with antirheumatic effects similar to those produced by cortisol. Wilkins, Gardner, Crigler, Migeon and Silverman have administered hydrocortisone to a child with congenital adrenal hyperplasia with androgen-suppressive effects equivalent to cortisol. The latter workers have also administered corticosterone (compound B) to one infant with the Na-losing type of congenital adrenal hyperplasia. There resulted an improvement in Na retention and partial suppression of the excess androgens.

In view of the increasing multiplicity of these therapeutic agents in pediatrics, let us review some of the knowledge concerning their physiologic effects.

Intermediary Metabolism of Carbohydrate, Protein and Fat

Twenty years ago Britton and Silvette at the University of Virginia discovered that the administration of adrenal extracts to normal and adrenalectomized animals produced an increase in the concentrations of blood sugar and liver glycogen. These experiments were amplified by Long, Katzin and Fry at Yale, who published their definitive study in 1940 (Endocrinol. 28:309, 1940). These workers found that the administration of adrenal extract or crystalline 11-oxygenated steroids (cortisone, hydrocortisone and corticosterone) caused an increase in the concentrations of blood sugar and liver glycogen, and an increased urinary N excretion. Their animals showed an absolute increase in body carbohydrate and a decrease in respiratory quotient as measured by the Haldane device. Thus there appeared to be a slowing down in the oxidation of glucose, together with an increase of gluconeogenesis from protein. Later Li, Simpson and Evans found that there was an absolute increase in body fat of rats treated with ACTH. Clinical studies in man by less direct methods have borne out most of these findings. Whether there is a negative N balance in man seems to depend upon appetite, since some patients on large doses of ACTH or cortisone maintain a positive N balance in the face of excess urinary N loss by voluntarily increasing their food intake. As F. L. Engel has pointed out (Am. J. Med. 10:556, 1951), the possibility exists that the hyperphagia which frequently accompanies ACTH or cortisone therapy represents a homeostatic response by the body to prevent undue N loss.

Electrolyte Metabolism

There is great variation among adrenal steroids in their respective influences on electrolyte and organic metabolism.* Desoxycortisosterone (DCA) is potent in causing urinary Na retention and K excretion, but it has essentially no effect on carbohydrate metabolism. Corticosterone occupies an intermediate position. It has some DCA-like effect on Na and K, and in addition has an influence on carbohydrate metabolism. At the other extreme both cortisone and hydrocortisone have relatively little Na-retaining effect, but have a very marked carbohydrate effect. In the presence of an intact adrenal cortex, ACTH is quite effective both on electrolyte and carbohydrate metabolism.

The continued administration of cortisone or ACTH may result in cumulative K deficiency. K deficient animals show myocardial lesions, electrocardiographic changes and replacement of intracellular K by Na, Mg and Ca. Serum K and Cl concentrations are low, and serum CO2 concentration is high. In such animals chronic diarrhea may develop. The administration of K rapidly corrects the metabolic abnormalities.

Most of the above findings have been described in patients with chronic K deficit, and the administration of K parenterally or by mouth has been beneficial.

Detection and Management of Adrenal Hormone Toxicity

It should be pointed out that toxic effects are most likely to be seen in those diseases which require a therapeutic dose level of ACTH or cortisone that approaches the toxic level. Rheumatoid

* The relationships of chemical structure to physiologic action of adrenal steroids were outlined in a previous Panel Discussion: The Adrenal Gland in Health and Disease, A. W. Jacobsen, Chairman, Pediatrics 3:515, 1949.
arthritis, rheumatic heart disease and the hypersensitivity syndromes are examples of this group. On the other hand, an entirely different mode of action of cortisone appears to obtain in congenital adrenal hyperplasia, so that fortunately in that group of cases the effective dose of cortisone is usually well below the toxic level.

Some of the metabolic abnormalities previously described may serve as aids in appraising the clinical state of children on chronic therapy with ACTH or the 11-oxygenated steroids.

1. Disordered Carbohydrate Metabolism: If a diabetic child is given ACTH or cortisone for any reason, one should expect an immediate increase in insulin requirement. In nondiabetic children disturbances of carbohydrate metabolism on hormonal therapy have been rare.

2. Disordered Protein Metabolism: The maintenance of proper N balance in a growing child on chronic ACTH or cortisone therapy poses a serious problem not encountered in adult patients, since somatic growth is a sensitive reflection of N balance. Because these hormonal agents may produce negative N balance if N intake is not adequate, the pediatrician must watch carefully the appetite and food intake of such patients, especially the protein intake. In infants and children receiving ACTH or cortisone, the use of testosterone to enhance N balance is contraindicated. Periodic measurement of longitudinal growth, body weight, and bony maturation by x-ray are simple, objective procedures which aid in estimating clinical progress.

3. Disordered Electrolyte Metabolism: Fluid retention with edema is often the first sign of K deficit in patients receiving ACTH or cortisone. A daily chart of fluid intake-output is useful in predicting trouble. When such patients develop low serum Cl and increased serum CO₂ concentrations, K deficit is a virtual certainty. The finding of a low serum K concentration is confirmatory, although more difficult technically. Electrocardiographic abnormalities, such as low or inverted T-waves, depressed ST segments and prolonged QT interval may develop. If dietary Na restriction is ineffective, the addition of 0.5 to 3 gm. KCl by mouth each day may be helpful.

Summary

The administration of ACTH or 11-oxygenated steroids to animals results in: (a) increased blood sugar and liver glycogen concentrations, partially as a result of decreased glucose oxidation; (b) increased urinary N excretion; (c) increased total body fat, and (d) tendency toward Na retention and K deficit. In clinical studies these findings have been largely confirmed, using indirect technics. Children on long-term treatment with full doses of adrenal hormones present a special problem, since the foregoing metabolic abnormalities cause inhibition of somatic growth. Periodic clinical appraisal of these patients with careful longitudinal measurements, body weight and x-rays for bony maturation are suggested. The importance of a food intake adequate to offset a negative N balance is stressed, as well as the provision of added K to prevent chronic K deficiency.

Question: How soon after you start treatment does K deficiency develop? That is, if you are using cortisone.

Dr. Gardner: Compared with desoxycorticosterone, cortisone is a relatively weak K depleting agent, and the development of clinically measurable K deficiency on full doses of cortisone may take several weeks or even longer. This variability of K depleting effect may depend to a great extent upon the dietary intake of Na, since K deficit appears to develop much more readily in the presence of adequate or more than adequate Na intake.

Chairman Najjar: In bringing this discussion to an end, I would like to repeat some of the highlights presented here. We know now that some cases of hypoglycemia show absence of the alpha cells of the islet tissue of the pancreas. When pancreatic tissue is obtained under circumstances requiring surgical exploration, one must look for the alpha cells. These cells excrete a hormone, here-tofore unsuspected, the hyperglycemic hormone. This is in the process of being produced commercially and should be available in the future. This hormone may well have the therapeutic potentialities for those cases, as insulin has for diabetic patients. Cases with glycogen disease may show severe and irreversible hypoglycemia. Some cases show abnormal glycogen and there is a good possibility that a defect in the enzyme system is responsible. Hormones play a significant role in carbohydrate metabolism and, when uncontrolled, may have a deleterious effect as witnessed by the development of Cushing's syndrome following ACTH therapy.
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