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Metabolic and Renal Diabetes after Administration of ACTH

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It is well known from animal experiments that certain kinds of adrenal steroids and ACTH are able to produce a diabetic state. Only a few studies have appeared dealing with the effect of these compounds on carbohydrate metabolism in human beings—patients treated with Cortisone or ACTH.

About a year ago we published a brief paper (in The Scand. J. Clin. a. Labor. Invest.) in which it was shown that the administration of ACTH in two patients had caused a metabolic as well as a renal diabetes. Since then we have further investigated this problem. I should like to-day to show some of the results of these studies.

The first slide (fig. 1) shows the average values of ordinary glucose tolerance curves from 21 patients without any disturbance of the carbohydrate metabolism with and without ACTH. Glucose tolerance test was first made and 3 days later 40 mg of ACTH (Acton) were given one hour before the administration of glucose. The average curve with ACTH is higher and more prolonged than that from the experiments without ACTH. However, on statistical analysis no significant difference is found between the corresponding points on the two curves.

It is clear, therefore, that other conditions must be applied to demonstrate a possible action of ACTH in therapeutic doses on carbohydrate metabolism.

For this purpose another kind of experiment was undertaken. The following slides will show the results. In these the patients were studied in a preceding control period, an ACTH period in which 60–200 mg of ACTH were given in 3–5 daily doses, and in a final control period. Diet and muscular activity were standardized as closely as possible. The patients were confined to bed, except for one hour daily at the same time of the day, in which they were allowed to walk in the corridor. The diet was composed in such a manner that it contained the same amount of carbohydrate, fat and protein per meal every day during

[1] Read by C. Holten.

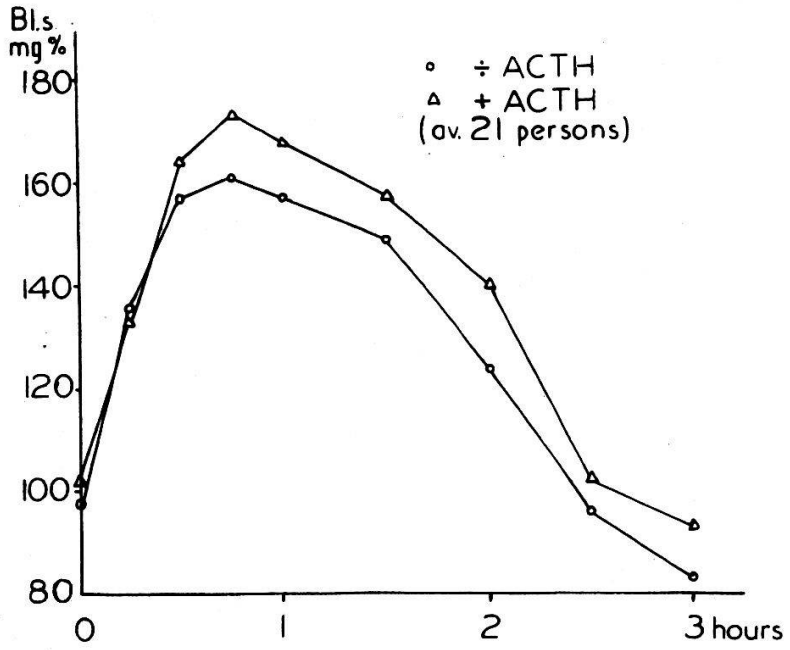

Fig. 1.

the entire period, the meals were served to the minute, and the patients were urged to eat the whole meal. Breakfast included 70 g of glucose every day. The total caloric content of the diet per day was calculated on the basis of the predicted basal metabolism plus 40% for activity, specific dynamic action, etc.

In this way glucose tolerance curves were obtained every day during the three periods. Blood sugar was determined before and one, two, and three hours after breakfast. The total amount of sugar excreted in the urine per 24 hours was daily determined. In some of the experiments serum inorganic phosphate was estimated before and two hours after breakfast as an indication of peripheral glucose utilization.

The next slide (fig. 2) gives the results of such an experiment. The patient was a 40 year old man, suffering from ankylosing spondylitis. The upper section of the graph shows the fasting blood sugar. No change occurs when ACTH (100–60 mg per day) is administered. On the next section the maximal blood sugar is seen, i.e. the highest blood sugar value observed each day of the whole period. Here again we find that ACTH is without appreciable effect. The next three sections show the blood sugar values one, two, and three hours after ingestion of glucose, calculated as per cent of the fasting blood sugar value. Here we find the first hour blood sugar a little lower, but higher values in the second and in the third hour blood sugar during the ACTH period. This means that the declining parts of the glucose tolerance curves on the days when ACTH is given are less steep than in the control periods, i.e. a metabolic diabetogenic effect of ACTH.

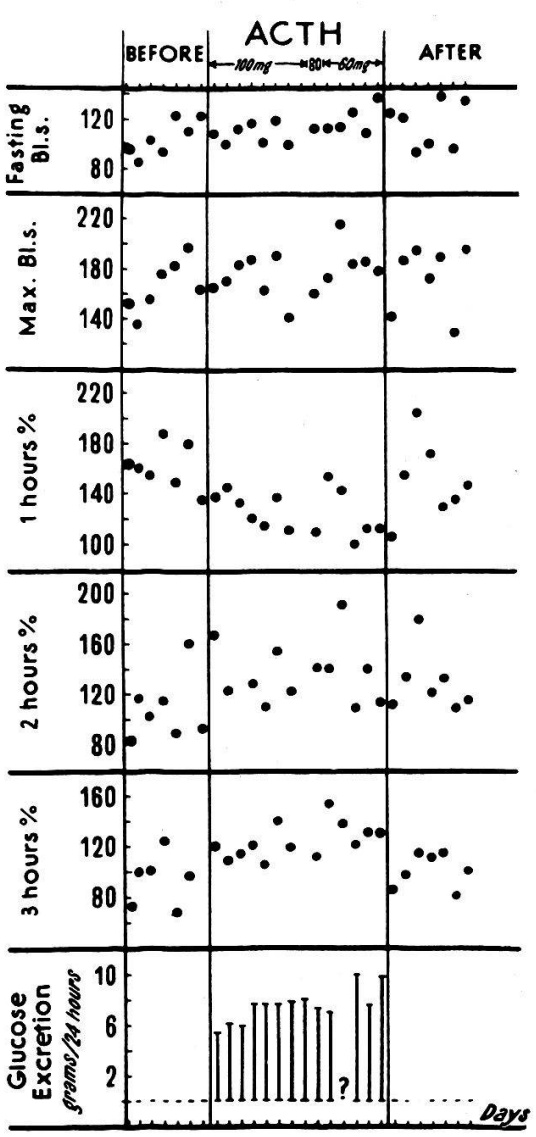

Fig. 2.

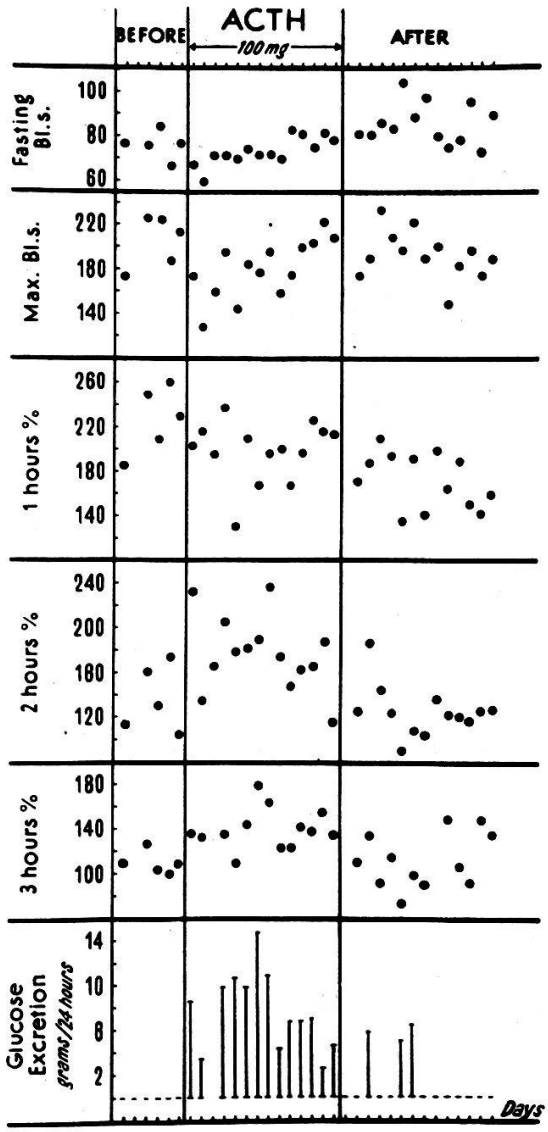

Fig. 3.

The columns in the lowest section show the excretion of glucose in the urine. It is seen that a severe glycosuria appears in the ACTH period. As the fasting and the maximal blood sugar values are unchanged, this means that a renal diabetes has been provoked along with the slight metabolic diabetes.

The next slide (fig. 3) is from a 43 year old man with the same disease. It shows essentially the same order of events during the administration of ACTH: no change in fasting and maximal blood sugar, no change of the first hour blood sugar, rise of the second and third hour blood sugar, and a considerable glycosuria.

On the following slides the fasting and maximal blood sugars are left out, no changes occurring. In addition to the first, second and third hour blood sugar and the urine glucose, these slides show the fasting serum inorganic phosphate, the phosphate values 2 hours after ingestion

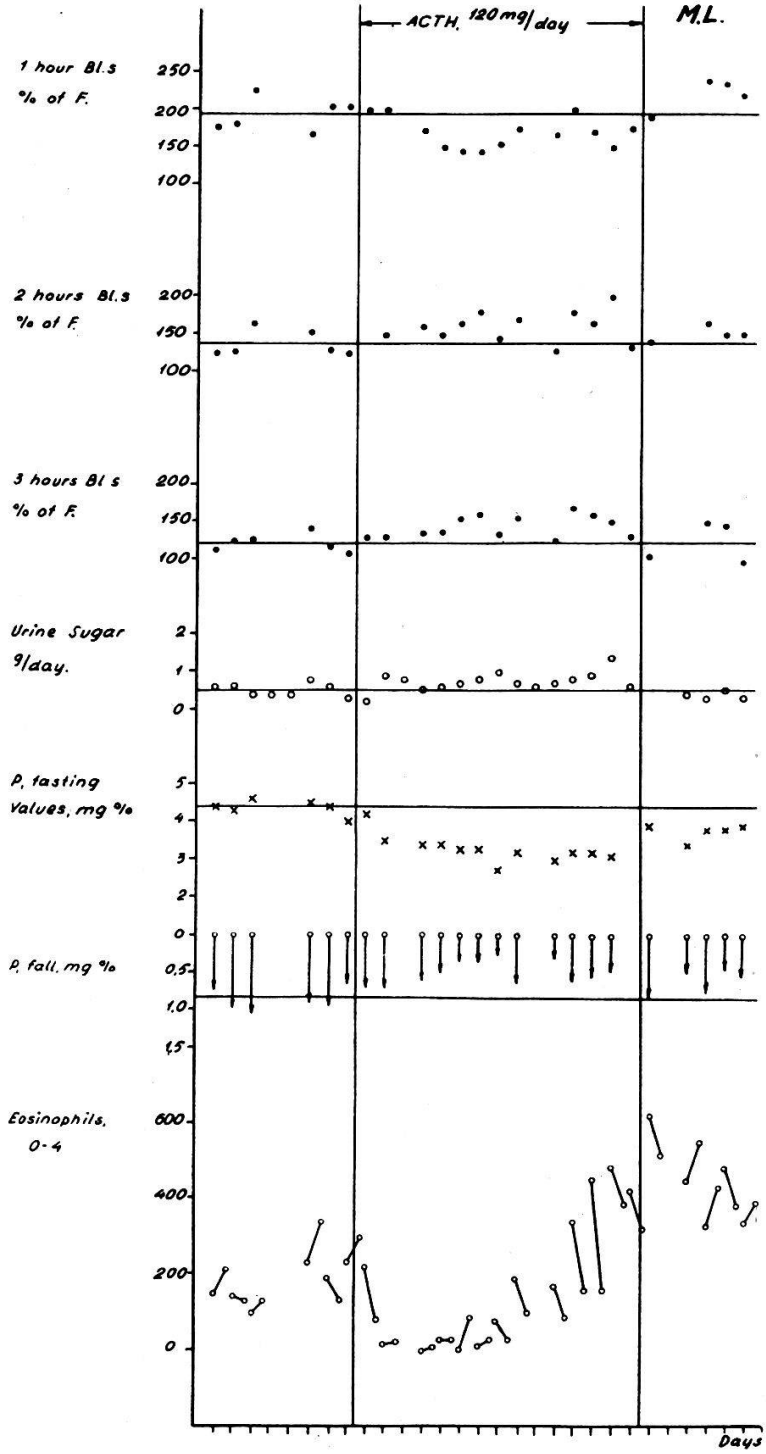

Fig. 4.

of glucose, which are lower than the fasting values, and the eosinophils before and 4 hours after the morning dose of ACTH.

The first of these slides (fig. 4) is from a 55 year old man with psoriatic arthritis. A depression is seen of the first hour blood sugar, slight elevation of the second and third hour blood sugar (the horizontal lines on this and on the following slides are different from the two previous ones as they correspond to the average value of the control period preceding

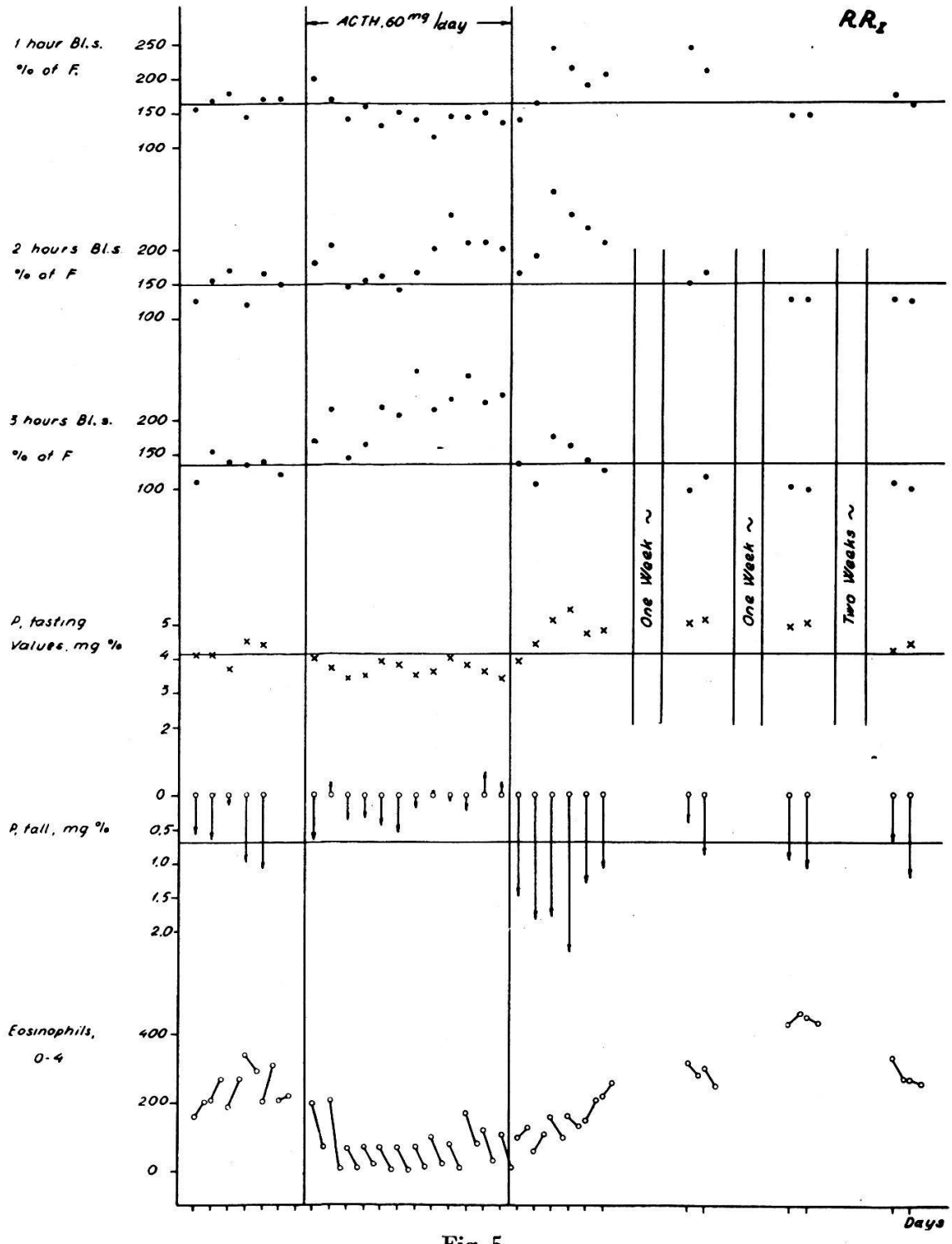

Fig. 5.

the ACTH period. There is no glycosuria. Fasting inorganic phosphate is lower in the ACTH period, and the phosphate fall after glucose is less than in the control periods.

The next slide (fig. 5) is from a 44 year old man, suffering from rheumatoid arthritis. Here a more pronounced metabolic diabetes is provoked, as it appears from the elevation of the second and third hour blood sugar values. Urine sugar is not shown, as there was no glycosuria. The fasting

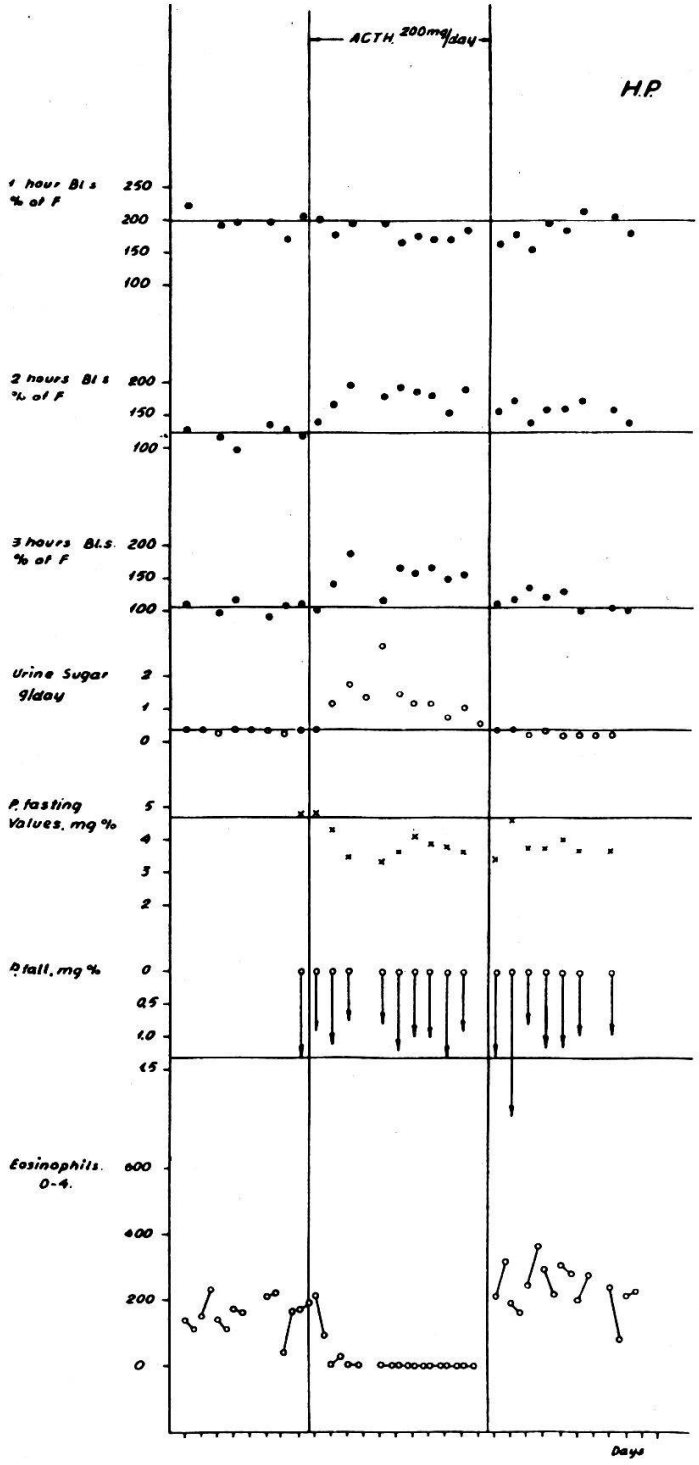

Fig. 6.

serum inorganic phosphate is low, and the fall of the phosphate after glucose is very strongly inhibited in the ACTH period. After stopping ACTH, in the second control period, the fall of serum phosphate is increased, the differences between values before and after glucose being strikingly large.

The last slide (fig. 6) shows the results of a larger dose of ACTH, 200 mg per day, in a 50 year old woman with rheumatoid arthritis. In this case

also a rather pronounced metabolic diabetes resulted, but here a renal effect was obvious, too. Fasting and maximal blood sugar values (not shown) were *not* elevated in the ACTH period. Unfortunately, serum inorganic phosphate was only determined on one day before the ACTH period. It seems, however, as if the lowering of the values during the period of treatment had occured here just as in the other experiments. It is perhaps wise not to make any statements about the fall of the phosphate in this experiment.

We have several other experiments, which gave about the same results, more or less distinctly, but time does not permit me to detail my subject.

It is obvious from most of the diagrams that the influence of ACTH on carbohydrate metabolism does not abruptly end with the discontinuance of ACTH, on the contrary, it may be rather pronounced for some time after (see e.g. fig. 2, 5, 6), but we have seen no instance where the ACTH effect has persisted.

In summary we may say that during the administration of therapeutic doses of ACTH there occurs a slight or moderate metabolic diabetes as disclosed by the delayed fall of the glucose tolerance curve.

No change in fasting blood sugar is found.

The result of the phosphate studies in some of the patients seems to indicate that the metabolic diabetes is caused, at least partially, by a decrease of peripheral glucose utilization.

In some cases a renal diabetes is superimposed upon the metabolic diabetes.

The disturbance of carbohydrate metabolism is reversible, and no permanent damage seems to be caused by ACTH in therapeutic doses.

Discussion:

S. Bonfils (Paris): Deux travaux français récents, actuellement sous presse (*Coste, Bonfils, Delbarre, Civatte; Gros, Bonfils, Machebœuf*) ont permis de préciser et d'interpréter certains de ces troubles métaboliques. La mesure simultanée de la glycémie et de la pyruvicémie au cours de l'épreuve de tolérance au glucose fut employée: alors que chez les sujets normaux les deux courbes sont parallèles, et que chez le diabétique la pyruvicémie ne s'élève pas, on peut noter de manière constante sous l'action du traitement cortisonique (ou ACTH) une élévation considérable de la courbe de pyruvicémie, alors même que la glycémie est normale.

Etudiée au cours de nombreux états pathologiques, l'épreuve n'a révélé ce trouble qu'au cours des syndromes d'hyperfonctionnement adrénocortical (*Cushing-Apert*) et au cours des hépatites.

Etant donnée l'action favorable des ictères infectieux sur les douleurs des rhumatismes chroniques inflammatoires, on pourrait donc supposer qu'une ou plusieurs des actions de la Cortisone sont sous la dépendance d'une action directe de l'hormone sur le foie.

Bien qu'il n'existe pas d'altérations morphologiques des cellules hépatiques, il a été montré qu'à ce niveau il existe une diminution considérable de l'acide désoxyribonu-

cléique (rapporté au poids d'azote du tissu), qui ne se retrouve dans aucun autre organe, ni même dans le tissu lymphoïde.

Un des moyens de préciser l'action de la Cortisone paraît donc bien d'étudier les troubles métaboliques qu'elle provoque.

B. Rose (Montreal): These findings are interesting in comparison with those of *McAlpine* and *Hoffman* who showed a very definite impairment of the CHO tolerance in normal subjects during ACTH administration.

During the administration of ACTH or Cortisone to patients with Diabetes Mellitus along with allergic manifestations such as severe rhinitis or asthma, we have found that the diabetic state is further increased, but this is temporary in nature. Thus, in such patients treated with continuous ACTH or Cortisone for a period of eighteen (18) months or longer, no evidence of increase in the diabetic state beyond that which might normally be expected was produced.

G. Sala (Milano): We have studied in collaboration with *Cavallero* and *Ballabio* the influence of Cortisone on carbohydrate metabolism in normal and diabetic man and in normal and diabetic rat. Cortisone aggravated the diabetes both in man and in the animal. The hormone did not impair carbohydrate metabolism in normal man and animal. In fact glucose tolerance test and insulin sensitivity were normal before and after the treatment (in men 100 mg daily for 10 days, in rat 5 mg daily for 20 days); serum inorganic phosphate decreased under the action of insulin before and after the treatment. In the rat we noted an increase of the mitoses in the β-cells of endocrine pancreas. We think that cortisone may be diabetogenic only when the organism has lost its homeostatic mechanisms of regulation, as it happens in diabetes. We have observed a decrease of glucose Tm in one woman treated with Cortisone, as expression of reduced glucose renal threshold.