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Glucose-stimulated Insulin Secretion during "Remission" of Juvenile Diabetes* **

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Summary. "Remission" of overt juvenile diabetes is a rare phenomenon, usually of only transient duration. In 4 subjects, aged 7.5 to 12 years, treated only with diet for almost a year, studies of glucose tolerance and insulin secretion following oral glucose (OGTT) and glucose- plus glibenclamide application were performed at different intervals after the onset of diabetes. Initially, no difference of response was observed between these and other diabetic children, who turned out to depend on exogenous insulin from the beginning. 3 to 5 months later, a small, but insignificant elevation of glucose-induced insulin levels was observed, while lower glucose fasting values and a significant decrease of the glucose area were measured. This evidence seems to indicate an increased insulin activity or a higher peripheral insulin sensitivity as important factors effective during this period. Sulphonylurea application, together with glucose, diminished to a small extent the glucose area without stimulating insulin release. This effect may represent an extrapancreatic action of the drug. Shortly before permanent insulin treatment was required by 3 of the 4 subjects, no insulin elevation during OGTT was noticed.

Réponse insulinique à l'administration orale de glucose pendant la période de «rémission» de jeunes diabétiques

Résumé. Une «rémission» du diabète sucré juvénile est rare et en général passagère. Dans l'étude présente, la tolérance au glucose ainsi que la réponse de l'insuline plasmatique après glucose par voie buccale (OGTT), seul ou avec glibenclamide, ont été étudiées chez quatre enfants, âgés de 7.5 à 12 ans, traités seulement par le régime pendant presqu' une année, à différentes périodes après la manifestation du diabète. Au début, aucune différence ne pouvait être observée entre les réponses de ces sujets et celles d'autres jeunes diabétiques, qui devaient être traités par l'insuline dès la manifestation. 3 à 5 mois plus tard on a observé au cours de l'OGTT une petite élévation de l'insuline plasmatique, mais qui n'était pas significative, tandis qu'on notait des valeurs de glucose à jeun plus basses et une diminution significative de l'aire du glucose. Par conséquent, une augmentation de l'activité de l'hormone ou bien une élévation de la sensibilité périphérique envers l'insuline pendant cette période peuvent être discutées en tant que facteurs importants. L'administration de glibenclamide avec le glucose ne provoquait qu'une légère diminution de la glycémie, sans aucune influence sur les concentrations plasmatiques de l'insuline. Cette observation pourrait indiquer un effet extrapancréatique de la substance. Peu avant qu'un traitement permanent par l'insuline ne s'avère nécessaire chez 3 de ces 4 sujets, l'insuline plasmatique ne répondait plus à la stimulation glucosée.

Glucose-stimulierte Insulinsekretion bei jugendlichen Diabetikern während der „Remissionsphase"

Zusammenfassung. „Remissionen" des kindlichen Diabetes sind seltene Ereignisse. Bei 4 solchen Kindern im Alter zwischen $7^1/_2$ und 12 Jahren, während fast eines Jahres nur mit Diät kompensiert, wurden Glucosetoleranz und Insulinausschüttung nach oraler Glucose allein (OGTT) bzw. nach Glucose plus Glibenclamid in verschiedenen Zeitabständen nach der Manifestation untersucht. Anfangs konnte kein Unterschied zwischen diesen und anderen, primär insulinpflichtigen diabetischen Kindern festgestellt werden. 3 bis 5 Monate später wurde eine geringe, im Mittel jedoch insignifikante, Erhöhung der glucosestimulierten Plasmainsulinkonzentrationen registriert, während die Blutzuckernüchternwerte und die Glucosefläche nach oraler Gabe signifikant unter die bei insulinbedürftigen Diabetikern gemessenen Werte absanken. Diese Tatsache scheint auf eine Verbesserung der Insulinwirkung oder eine Erhöhung der peripheren Insulinempfindlichkeit als in dieser Phase wirksame Teilfaktoren hinzudeuten. Die zusätzliche Gabe des Sulphonylharnstoffs verminderte geringfügig die von der Glucosekurve umschlossene Fläche, ohne die Insulinausschüttung zu beeinflussen. Dieser Befund könnte auf einen extrapankreatischen Effect der Substanz zurückgeführt werden. Kurz bevor die Insulinbehandlung bei 3 der 4 Probanden erforderlich wurde, ließ sich eine Plasma-Insulinerhöhung im OGTT nicht mehr nachweisen.

Key words: Juvenile diabetes, plasma insulin, remission, oral glucose tolerance, glibenclamide.

Childhood and juvenile diabetes is considered to depend upon an absolute insulin deficiency [36]. Usually no plasma insulin elevation is observed following oral or intravenous glucose and sulphonylurea loads [2, 5, 11, 13, 15, 33, 36, 47, 49]. An impairment of glucose-stimulated insulinaemia, however, does not seem to be a late, but a rather early symptom of the disorder, since it is found in still healthy monocygotic twins of diabetics [9] or other potential diabetics, like children of two diabetic parents [42]. The mechanisms, which finally lead to the decompensation of a probably longtime well compensated system and provoke overt diabetes, are still badly understood. In only about 40% of diabetic children some exogenous factor interfering with the balance of this system has been found [43].

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Although the rapid progression to ketoacidosis in the majority of diabetic children and juveniles necessitates continuous insulin treatment from the onset of clinical symptoms, it has long been recognized, that the hormone requirements may fall to minimal doses or nil during a brief postinitial phase of some days' or weeks' duration [6, 50], and that longerlasting "remissions" can occur in children [1, 25, 28, 29, 34, 46] and in adults with the juvenile type of diabetes [7, 12, 14, 16, 19, 22, 26, 27, 29, 34, 44, 45]; a recent review of the literature on remission of diabetes is given by Pirart and Lauvaux, 1971. In some such cases even the diabetogenic stress of pregnancy has been tolerated without any need for insulin treatment [7]. In others, overt diabetes remains compensated on diet alone for a varying length of time without any necessity for even temporary insulin treatment [26, 27, 32].

While most of the above mentioned reports refer to remissions during the immediate postinitial period of the disorder [1, 25] or after a short-term insulin treatment up to 3 years [7, 12, 17, 19, 22, 34, 45], Hines and Kessler have published the history of a woman, who, after a 21-year-period of insulin treatment, showed a permanent restoration of a normal glucose tolerance, which was maintained even during surgical stress. Certainly, this case will remain a rare exception.

In view of the pathogenesis of the disease, studies on insulin secretion in these stages deserve special interest. Only few have been reported so far [1, 17, 22, 25, 26, 27, 32], demonstrating controversial results, with a partial restitution of insulin response to glucose or other insulin-releasing substances [17, 22, 26, 32] or no response whatsoever [1, 25]. It has to be noted, however, that these studies have been performed at different intervals after the onset of diabetes, partly during the initial phase [1, 25], partly during well established clinical remission [17, 22, 26, 32]. Therefore, they may not necessarily be comparable.

The scarcity of information on this matter may make it worthwhile to report on insulin secretion in some such patients during "remission", as a contribution to the still non-resolved question, whether or not

Table 1. *Data of diabetic children, treated with diet only*

	F.A. ♂	D.K. ♀	K.D. ♂	M.A. ♂
Age at onset of diabetes (ys)	8	7.5	9.3	12
Overweight (%)	±0	+40	+33	+27
Initial glucose excretion	+++	+++	+++	++
Ketonuria	+++	(+)	(+)	Ø
Period without insulin (mo)	11	10	11	15 (cont.)
Growth dur. this period (cm)	4.5	3.0	5.0	8.0
Weight changes (kg)	+1.0	−7.5	−7.5	−1.5

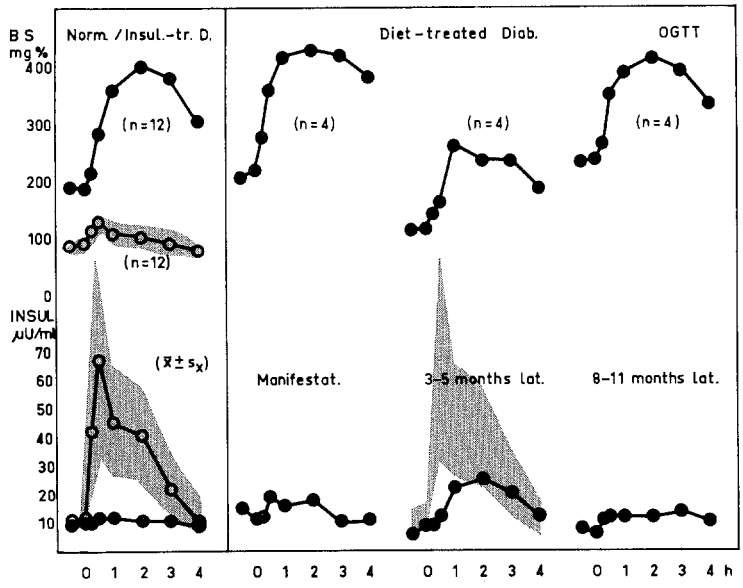

Fig. 1. Glucose- (upper part) and insulin-values (lower part) during OGTT of 4 diet-treated diabetics (right segment) at different intervals after manifestation, compared to the responses of non-diabetic (open circles, mean ± 1 SD) and insulin-dependent diabetic children (closed circles; left segment)

a partial recovery of the pancreatic responsiveness to physiologic stimuli is responsible for the favorable clinical course of the disorder during this period.

Material

We have been able to follow four children aged 7.5 to 12 years, who were hospitalized in 1970 with symptoms of overt diabetes. Three of them were obese and had little or no ketosis. Some relevant data of these subjects have been summarized in Table 1.

The clinical observation that diet alone — in the obese subjects restriction of calories — within a few days fairly well compensated the metabolic disorder (only in F.A. augmented by an initial 12 days' insulin administration), seemed to indicate a relatively benign course of the disease. In each of the children, insulin could be withheld for almost a year. Oral glucose tolerance tests (OGTT) were performed at different intervals following the onset of diabetic symptoms: initially (test A), 3 to 5 months (test B), and 8 to 11 months later (test C). On each occasion on two subsequent days either glucose alone (2 g/kg body weight), or glucose + glibenclamide (5 mg-tablet per person at time 0) was administered. 12 non-diabetic children and 12 primarily insulin-dependent diabetics served as controls.

Blood sugar was measured by the ferricyanide method of Hoffman with a Technicon autoanalyzer, plasma insulin by radioimmunoassay (modification [39] of the Hales and Randle method [18]).

Results

Glucose tolerance and insulin values at presentation of diabetes (A) in these 4 subjects do not differ from those of diabetic children who require insulin either continuously from the beginning or after a short insulin-free post-initial phase. After a 3 to 5 months' period of either restricted (obese) or normal diet (F.A.) containing about 50% carbohydrates, 35% fat and 15% protein without any other treatment, fasting blood sugar values are almost normal (B). Following the glucose load, the mean blood sugar maximum is 263 mg% as compared to 429 mg% during the first investigation. It occurres earlier, at one hour rather than at two hours after ingestion. Nonetheless, the curve is undoubtedly diabetic, exhibiting 2hr- and 4hr-values of 236 and 188 mg%, respectively.

A small, sustained rise of the mean plasma insulin concentration reaching a late maximum at 2hr (compared to peak values at 30 min in control children) is observed only during this period, 3 to 5 months after diabetes manifestation (B). No change of basal values after glucose is seen at presentation (A), as in the insulin-treated group. During the latter half of the second test (B), insulin concentrations overlap with the one-standard-deviation-range of normal children, which during the preceding investigation is never reached.

Several months later (C), shortly before insulin treatment becomes necessary in 3 of the subjects (except M.A., s. Table 1), glucose and insulin values resemble those of primarily insulin-treated children.

When — for reasons of easier comparison — the total areas under the individual blood-sugar and insulin curves are calculated and matched, significant differences exist between normal and diabetic children for both parameters (Fig. 2).

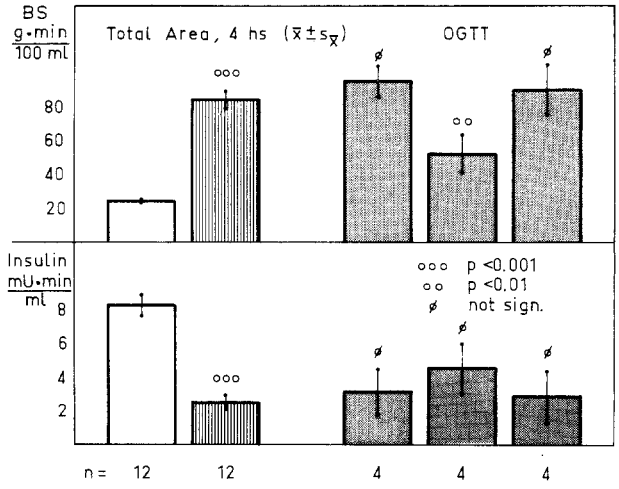

Fig. 2. Blood sugar and insulin areas of (from left to right) normal, insulin dependent diabetics (id) and diet-treated diabetic children (dt) at presentation and 3 to 5 as well as 8 to 11 mo. later. Significance of differences was calculated between normal and diabetics (id), and between id and dt subjects

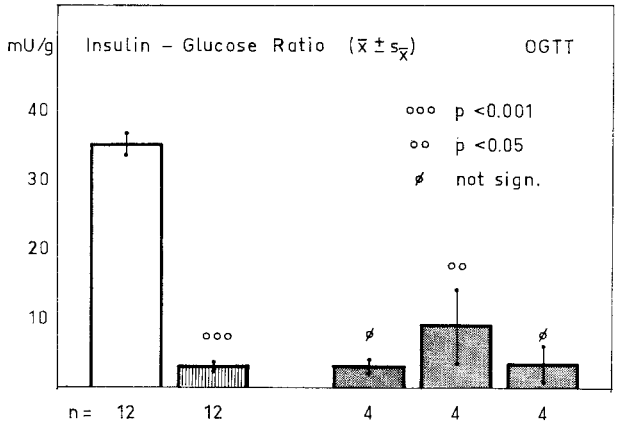

Fig. 3. Insulin-glucose ratio. The different columns represent the same children as in Fig. 2

Compared to the insulin-treated diabetics, however, the non-insulin-requiring children show significant differences only of glucose values during the second investigation period (B). The somewhat higher insulin output at this stage is not statistically different from that of the insulin-treated group.

The insulin-glucose ratio (Fig. 3), calculated from the individual areas of both parameters, only at this period (B) demonstrates a significant mean difference from of primarily insulin treated subjects. Nevertheless, this value is only about one fourth of that in normal controls, indicating a highly in-

sufficient insulin release. This is most evident in Fig. 4, which compares the glucose-, insulin-, and insulin/glucose-areas of the eldest subject, who managed to achieve a temporarily normal glucose tolerance within 7 months after the onset of diabetes, with the respective values in the control group.

When glucose and glibenclamide are given simultaneously, normal as well as diabetic subjects of both groups exhibit a small decrease of the total glucose

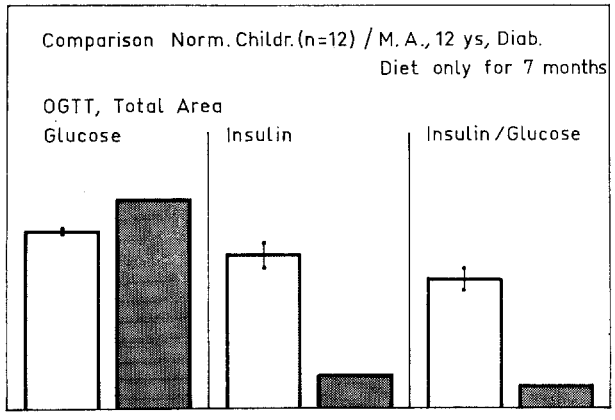

Fig. 4. Comparison of glucose-, insulin-, and i/g-areas of M.A. (hatched columns) versus non-diabetic children (white columns)

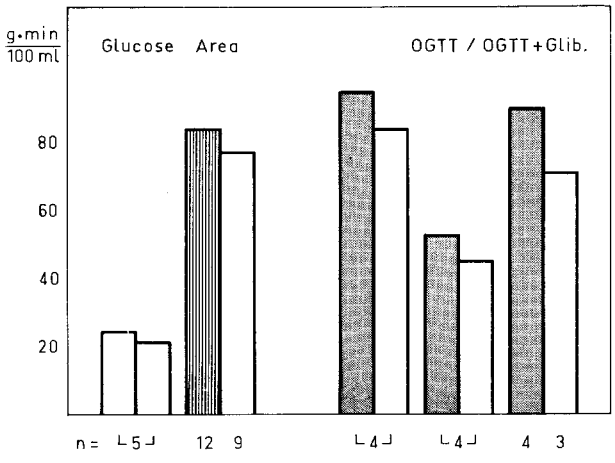

Fig. 5. Effect of glibenclamide on glucose areas (white half-columns) compared to glucose-areas of OGTT (dark columns). The different groups are presented as in the preceding figures

area (Fig. 5). The existing group differences are not influenced. In normal children, this effect seems to be due to a faster decline of blood sugar values following the 30 min peak (Fig. 6). No striking changes of insulin values can be observed, except for a second peak at 2 h, presumably derived from the delayed effect of the drug following its slow intestinal absorption. Earlier investigations in fasting children have shown insulin maxima after glibenclamide administration at 90 min [48]. As in the controls, diabetic children do not exhibit consistent changes of plasma insulin values. The insulin-glucose ratio is not increased (Fig. 7) in those diabetics who still possess some insulin reserve (B). The slight elevations of this parameter in the non-responsive subjects seem to represent fluctuations of the basal line only.

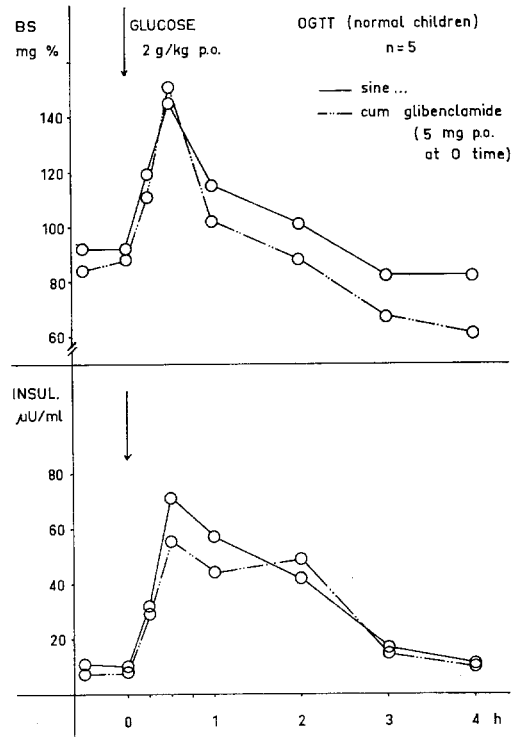

Fig. 6. Kinetics of blood sugar and plasma insulin values in normal children during OGTT and OGTT + glibenclamide

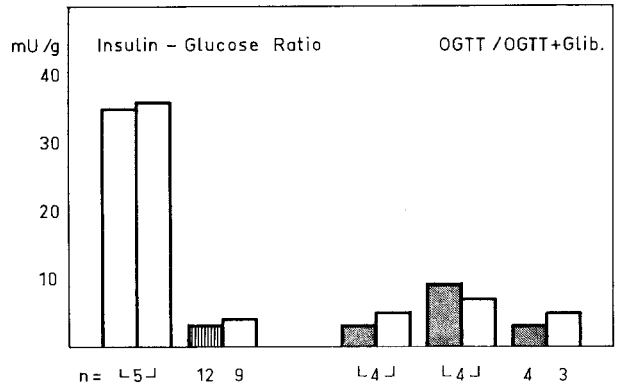

Fig. 7. Insulin-glucose ratios in normal an diabetic children during OGTT and OGTT + glibenclamide

Discussion

Different degrees of metabolic improvement following the manifestation of diabetes mellitus have been euphemistically called "remission". An exact evaluation of the term, however, would have to imply not

only a complete reversal of clinical symptoms, but also a normalisation of glucose tolerance. This, in fact, applies to only relatively few juvenile diabetics, e.g. those subjects reported by Hines and Kessler, Carlström and Ingemanson, and some of the cases of Lister. In the majority of subjects only "partial remissions" occur, leading to a temporary metabolic compensation without exogenous insulin. In these diabetics, glucose tolerance remains abnormal (e.g. cases of Harwood, Hernandez *et al.*, Johansen and Lundbaek, Kosaka *et al.* and Lister). Still another term, "early partial remission", has been applied to the well-known state of clinical improvement in diabetic children about a fortnight after the beginning of insulin therapy, coinciding with a significant reduction of insulin requirements and an amelioration, though not normalization, of glucose tolerance (Baker *et al.* [1]). It is doubtful, whether or not this latter term is justified, because at this stage of the disease its subsequent course cannot be foreseen. In fact, only one child out of Baker's series did not require exogenous insulin treatment for several months.

According to the above definition, only one of the 4 subjects in this study showed complete, but temporary remission, while the others exhibited partial remission only. Neither blood sugar nor insulin values of the first investigation (A) allowed a prediction of the subsequent favorable progress. Even obesity influenced neither basal nor glucose-stimulated insulin concentrations. Overt diabetes in these subjects was related to an absolute insufficiency of glucose-stimulated insulin release. Only the clinical remission, retrospectively, permitted a distinction between these and other diabetic children.

Nevertheless, some pancreatic reserve capacity for a minimal insulin response to physiologic stimuli does seem to be a prerequisite for the clinical amelioration in these children. Exogenous factors, which may be responsible for the acute breakdown of carbohydrate metabolism in juvenile diabetics, were found in only one subject (M.A.), who experienced a well-defined disease (rubella) prior to the onset of diabetes. In the others, no exogenous reason for loss and recovery of the pancreatic responsiveness was detected.

At which interval after the onset of overt diabetes a subnormal insulin release is resumed may depend upon the nature of the factor(s) responsible for the metabolic imbalance at this moment. In the obese children, the weight loss following a low calory diet may have been contributary to the rapid clinical remission. The lean subject required insulin for several days. Concerning the time of recovery of the insulin secretion, no systematic investigations have been done. In Baker's case [1], after 20 days some insulin increase during the 4th hour following glucose ingestion was present. In the subjects presented here no insulin release was observed during investigation A, usually performed on the second day after admission to the hospital. The second test (B) was done during well established clinical remission, showing a little improvement, but far from normalization of the insulin output. Very likely though, a glucose-stimulated increase of insulin values in plasma may have been measurable long before this time.

The better metabolic balance and the smaller impairment of glucose tolerance during test B, as compared to A, seems to be related to the higher amount of insulin released at this period. This corresponds well with the observation of Kosaka *et al.*, who showed an inverse relationship between glucose- and insulin-areas during 9 glucose tolerance tests in a 17 year old diabetic woman [32]. However, the amount of insulin released into the circulation following physiologic stimuli may not be alone responsible for the longterm partial remission, which is achieved in these diabetics with considerably less insulin than is usually delivered from the pancreas of normal subjects. In one of the children, a normal glucose tolerance was temporarily maintained (s. Fig. 4). As a working hypothesis, which might explain this phenomenon, a potentiation of the insulin effectiveness or an increase of the insulin sensitivity of glucose utilizing tissues may be discussed. Similar assumptions have been made by Cerasi and Luft [8], Kipnis [30], and Luft [35] regarding the insulin-glucose relations in non-diabetic adults [8] and children [10] who exhibit a pancreatic hyporesponsiveness to glucose infusion. In these "low-responders" some reduction of the K-value for peripheral glucose utilization was observed, when compared with the results in subjects with normal insulin output [35]. This may indicate the absolute dependence of peripheral glucose metabolism upon the amount of circulating insulin. However, a mathematical correlation between these two parameters in normal subjects has not been found by all investigators [21, 49, 51]. Moreover, studies in dogs revealed the maintenance of a normal K-value even 1 h after total pancreatectomy [31]. This indicates that the acute pancreatic insulin release may constitute only one, perhaps not even the most important factor for a normal peripheral glucose metabolism. Some authors consider tissue concentrations of insulin to be a more appropriate parameter of insulin action than the amount of circulating hormone. Its concentrations in lymphatic vessels, for instance, seem to correlate more closely to the impairment of glucose tolerance following pancreatectomy than do plasma levels [40].

Oral glibenclamide does not increase the glucose-induced insulin output in diabetic children, neither at presentation, nor during the partial recovery of beta-cell function. This is not surprising, if the very small response of control subjects to the combined ingestion of glucose and the sulphonylurea compound is considered (s. Fig. 6). In fasting, non-diabetic, children glibenclamide alone hardly increases plasma insulin concentrations [48]. Similar results have been obtained in adult subjects following oral tolbutamide application [4].

In normal children, the faster decline of blood sugar values following glucose plus glibenclamide ingestion could be attributed to the small increase of the pancreatic insulin secretion during the second hour (s. Fig. 6). Higher insulin concentrations in the portal vein reduce the hepatic glucose output. However, similar decreases in the glucose areas have also been observed in the diabetic children, who did not show an additional insulin increase in peripheral plasma following glibenclamide ingestion. The insulin-glucose area of these children remains uninfluenced by the sulphonylurea. Therefore, an extrapancreatic effect of glibenclamide under these circumstances cannot be excluded. An insulin-independent reduction of the hepatic glucose release [3, 20, 41] would constitute the most probable explanation for the observation.

In conclusion, "remission" of overt juvenile diabetes does seem to require the recovery of a minimal beta-cell responsiveness to physiologic stimuli. The insulin effect may be enhanced by an increased peripheral sensitivity for the hormone, comparable to the effect, which has been assumed in so-called "low-insulin-responders" with still normal glucose tolerance. In the acute experiment, glibenclamide does not influence the glucose-stimulated insulin release of diabetic children, even during remission. Its small effect on blood sugar concentrations therefore may constitute an extrapancreatic action.

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References

1. Baker, L., Kaye, R., Root, A.W.: The early partial remission of juvenile diabetes mellitus. J. Pediat. **71**, 825–831 (1967).
2. De Belle, R., Belmonte, M.M., Colle, E.: Effect of intravenous tolbutamide in juvenile diabetes mellitus. Diabetes **16**, 215–218 (1967).
3. Bellens, R.: Contribution à l'étude des mécanismes d'action des drogues hypoglycémiantes. Acta endocr. Supl. 61, acc. Vol. **38** (1961).
4. Berchtold, P., Büber, V., Meier, V., Felber, J.-P., Keiser, G.: Vergleichende Untersuchungen über den oralen und intravenösen Tolbutamidtest. II. Bestimmung von Glucose, Serum-Insulin und Serum-Tolbutamid bei normalen, jungen Probanden. Diabetologia **7**,77–81 (1971).
5. Berson, S.A., Yalow, R.S.: Some current controversies in diabetes research. Diabetes **14**, 549–572 (1965).
6. Brush, J.M.: Initial stabilisation of the diabetic child. Amer. J. Dis. Child. **67**, 429–444 (1944).
7. Carlström, S., Ingemanson, C.-A.: Juvenile diabetes with long-standing remission. Diabetologia **3**, 465–467 (1967).
8. Cerasi, E., Luft, R.: Further studies on healthy subjects with low and high insulin response to glucose infusion. Acta endocr. **55**, 305–329 (1967).
9. — — Insulin response to glucose infusion in diabetic and non-diabetic monocygotic twin-pairs. Genetic control of insulin response? Acta endocr. **55**, 330–345 (1967).
10. — — The occurrence of low insulin response to glucose infusion in children. Diabetologia **6**, 85–89 (1970).
11. Chiumello, G., Del Guercio, M.J., Bidone, G.: Effects of glucagon and tolbutamide on plasma insulin levels in children with ketoacidosis. Diabetes **17**, 133–135 (1968).
12. Csapo, G., Szücs, S.: Spontane Remission des Diabetes mellitus. Med. Klin. 180–181, 1962.
13. Drash, A., Field, J.B., Garces, L.Y., Kenny, F.M., Mintz, D., Vazquez, A.M.: Endogenous insulin and growth hormone response in children with newly diagnosed diabetes mellitus Ped. Res. **2**, 94–102 (1968).
14. Duncan, G.G.: Quoted by Harwood, R.
15. Ehrlich, R.M., Bambers, G.: Immunologic assay of insulin in plasma of children. Diabetes **13**, 177–181 (1964).
16. Gelfand, M., Forbes, J.I.: Quoted by Pirart, J., Lauvaux, J.P. (38).
17. Genuth, S.M.: Clinical remission in diabetes mellitus. Diabetes **19**, 116–121 (1970).
18. Hales, C.N., Randle, P.J.: Immunoassay of insulin with insulin antibody precipitate. Biochem. J. **88**, 137–146 (1963).
19. Harwood, R.: Severe diabetes with remission. New Engl. J. Med. **257**, 257–261 (1957).
20. Hasselblatt, A.: Biochemische Gesichtspunkte zur Erklärung der blutzuckersenkenden und antidiabetischen Wirksamkeit von Sulfonylharnstoffderivaten. Internist **7**, 369–374 (1966).
21. Heard, C.R.C., Henry, P.A.J.: Glucose tolerance and insulin sensitivity. Clin. Sci. **37**, 37–44 (1969).
22. Hernandez, A., Zorrilla, E., Gershberg, H.: Serum-insulin in remission of juvenile diabetes. Lancet **1968 II**, 223.
23. Hines, J.J., Kessler, D.L.: Unexplained remission of long standing severe diabetes mellitus. Ann. intern. Med. **55**, 314–316 (1961).
24. Hoffman, W.S.: A rapid photoelectric method for the determination of glucose in blood and urine. J. biol. Chem. **120**, 51 (1937).
25. Illig, R., Prader, A.: Remission of juvenile diabetes. Lancet **1968 II**, 1190.
26. Johansen, K., Lundbaek, K.: Plasma-insulin in mild juvenile diabetes. Lancet **1967 I**, 1257–1259.
27. — Ørskov, H.: Plasma insulin during remission in juvenile diabetes mellitus. Brit. med. J. **1969 I**, 676–680.
28. John, H.J.: Spontaneous disappearance of diabetes. J. Amer. med. ass. **85**, 1629–1631 (1925).
29. Joslin, E.P., et al.: Quoted by Pirart and Lauvaux [38].
30. Kipnis, D.M.: Does diabetes begin with insulin resistance? Lecture: International symposium on early diabetes. Marbella/Spain, October 1968.
31. Kosaka, K., Mizuno, Y., Ogata, Y., Kuzuya, N.: Studies of glucose metabolism immediately following total pancreatectomy. Diabetes **15**, 179–182 (1966).
32. — Hagura, R., Saito, R., Tsukamoto, F., Kuzuya, T.: Changes in plasma insulin and glucose tolerance in stable diabetes in a young woman. Diabetes **18**, 487–492 (1969).
33. Lestradet, H., Tichet, J., Ludwiczak, H., Deschamps, I.: L-insulinémie dans la période d'installation du diabète infantile et juvénile. Diabetologia **6**, 90–97 (1970).
34. Lister, J.: The clinical spectrum of juvenile diabetes. Lancet **1966 I**, 386–388.
35. Luft, R.: Development of diabetes mellitus in man. International Symposium commemorating the 50th anniversary of insulin, Jerusalem, October 1971.
36. Parker, M.L., Pildes, R.S., Chao, K.-L., Cornblath, M., Kipnis, D.M.: Juvenile diabetes mellitus, a deficiency in insulin. Diabetes **17**, 27–32 (1968).
37. Pfeiffer, E.F., Schöffling, K., Ditschuneit, H.: Der Wirkungsmechanismus der oralen Antidiabetika. Die

blutzuckersenkenden Sulfonylharnstoffe und Sulfonamide. In: Pfeiffer, E.F.: Handbuch des Diabetes mellitus, Bd. I, 637—684.

38. Pirart, J., Lauvaux, J.P.: Remission in diabetes. In: Pfeiffer, E.F.: Handbuch des Diabetes mellitus, Vol. II, 443—502.
39. Quabbe, H.J.: Modifikation der radioimmunologischen Insulinbestimmung nach Hales und Randle. Diabetologia **5**, 101—107 (1969).
40. Rasio, E.A., Hill, G.J., Soeldner, J.S., Herrera, M. G.: Effect of pancreatectomy on glucose tolerance and extracellular fluid insulin in the dog. Diabetes **16**, 551—556 (1967).
41. Schambye, P.: Quoted by Pfeiffer et al. [37].
42. Soeldner, J.S., Gleason, R.E., Williams, R.F., Garcia, M.J., Beardwood, D.M., Marble, A.: Diminished serum insulin response in genetic prediabetic males with normal glucose tolerance. Diabetes **17**, 17—26 (1968).
43. Struwe, F.E.: Zur Manifestation des Diabetes mellitus im Kindesalter. 5. Kongreß der Deutschen Diabetes-Gesellschaft, Bonn-Bad Godesberg, Mai 1970.
44. Stutman, L.J., Hayes, J.D.: Severe diabetes with remission. Report of a case. Diabetes **8**, 189—191 (1959).
45. Taylor, K.W.: Serum insulin in a case of severe diabetes mellitus showing remission. Brit. med. J. **1960 I**, 1853—1855.
46. Vague, J., Favier, G., Delboy, C.: Diabète infantile récent et non traité apparamment guéri depuis 4 mois par 75 gr de 2254 RP en 26 jours. Le Diabète **4**, 234 (1956). Quoted by Pirart and Lauvaux [38].
47. Weber, B., Helge, H., Sihombing, G.: Plasmakonzentrationen von Insulin und freien Fettsäuren bei juvenilen Diabetikern nach Belastung mit Tolbutamid und Glukagon. Arch. Kinderheilk. **177**, 139—146 (1968).
48. — Hahn, W.: Blutzucker- und Plasma-Insulinkonzentrationen bei Kindern nach oraler Gabe von Glybenclamide (HB 419). Z. Kinderheilk. **108**, 32—40 (1970).
49. — Plasmainsulin bei Kindern. Klinische Studien bei stoffwechselgesunden, adipösen und diabetischen Probanden. Beiheft 65 zum Arch. f. Kinderheilk. 1971.
50. White, P.: Natural course and prognosis of juvenile diabetes. Diabetes **5**, 445—450 (1956).
51. Williams, R.F., Gleason, R.E., Garcia, M.J., Soeldner, J.S.: Differences in the relationship between blood glucose (BG) and serum immunoreactive insulin (IRI) during rapid and slow glucose infusions. Clin. Res. **14**, 356 (1966).

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