

The Functional Significance of a Spontaneous Pancreatic Islet Change in Aged Rats

A. HAJDU, F. HERR and G. RONA

Department of Biology, Ayerst Research Laboratories and Department of Pathology,
The Lakeshore General Hospital, Montreal, Canada

Received April 14, 1967

Summary. A decreased glucose tolerance as compared with that of healthy young rats was found in male aged rats (52 weeks) of the Sprague-Dawley strain whose pancreatic islet morphology was normal. This abnormal pattern of tolerance was further exaggerated in rats with a spontaneous islet change (fibrosis and enlargement) described by us previously. These observations suggest that in aged rats a discrepancy between insulin demand and availability preceded the morphological changes of the pancreatic islets. Thus, the islet fibrosis and enlargement may be regarded as an expression of a failing compensatory adjustment.

Signification fonctionnelle du changement spontané des îlots pancréatiques chez les rats âgés

Résumé. Chez le rat de souche Sprague-Dawley (mâle) la tolérance au glucose était réduite chez le groupe âgé de 52 semaines relativement à celle des jeunes animaux bien que leurs îlots pancréatiques soient apparus histologiquement normaux. Cette diminution de la tolérance au glucose était encore plus sévère chez les rats du groupe âgé dont les îlots pancréatiques montraient certaines altérations morphologiques spontanées, que nous avons décrites précédemment (i.e. fibrose et hypertrophie). — Ces observations suggèrent que chez les rats âgés une disparité entre les demandes et les disponibilités insu-

liniques précède les altérations morphologiques des îlots pancréatiques. La fibrose et l'agrandissement des îlots pourraient être alors les manifestations de la défaillance du mécanisme d'ajustement compensatoire.

Funktionelle Bedeutung von Spontanveränderungen der Pankreas-Inseln bei älteren Ratten

Zusammenfassung. Ältere Ratten (52 Wochen alt) vom Sprague-Dawley Stamm, mit normaler Morphologie der Langerhans'schen Inseln, wiesen — im Vergleich mit gesunden jungen Ratten — eine herabgesetzte Glucosetoleranz auf. — Diese Toleranzstörung war noch ausgeprägter bei Ratten, welche eine — bereits beschriebene — Spontanveränderung der Pankreas-Inseln (Fibrose und Vergrößerung) erkennen ließen. Diese Befunde deuten darauf hin, daß bei älteren Ratten eine Diskrepanz zwischen Insulinbedarf und Verfügbarkeit besteht, welche den morphologischen Veränderungen der Langerhans'schen Inseln vorausgeht. Fibrose und Vergrößerung können deshalb als Ausdruck eines Versagens der ausgleichenden Anpassung gewertet werden.

Key-words: Islet of Langerhans, spontaneous islet change, Sprague-Dawley rat, age and sex predisposition, glucose tolerance, islet regeneration.

We have reported from this laboratory a high incidence of a spontaneous pancreatic islet change in adult and old male Sprague-Dawley (Charles River) rats [8]. This consisted of an intra- and peri-insular fibrosis and enlargement of the involved islets composed predominantly of beta cells while the alpha cells showed apparently normal distribution. It has been suggested that the islet change probably represents a compensatory adjustment of some unknown metabolic requirement in the adult and aging animals. In this paper the functional significance of this finding is reported as reflected by glucose tolerance studies.

Materials and Methods

One hundred, fifty-two week old male rats of the Sprague-Dawley strain (Charles River) were used. Ten, eight-week old male rats were used for comparative purposes. The intra-peritoneal glucose tolerance test was performed, according to the methods used by WEXLER and FISHER [13], and COLE and HARNED [3], (350 mg of glucose in a 10% solution per 100 g of body weight, after 18 hours of starvation, 0, 1/2, 1, 2, 3, 5 hour values). The result of the tests was evaluated statistically as well as according to the criteria set by

COLE and HARNED [3]. The conditions of normal values were as follows: 1. 1/2 hour value greater than 1st hour level. 2. 1/2 hour value less than 300 mg%. 3. 5th hour value at least 40 mg% below the 1/2 hour level. 4. 5th hour value below 180 mg%. After the 5th hour blood taking the rats were killed. The pancreas was processed for histological examination. On the basis of histopathological examination the animals were divided into two groups: "normal" (negative or only few islets with very slight fibrosis on the section) and animals with islet fibrosis and enlargement (the majority of medium and large islets is markedly fibrosed and enlarged or giant conglomerate islet is present).

Results

The histopathological examination of the pancreas sections revealed a 48% incidence of the above-mentioned spontaneous change of the islets. This alteration consisted of a marked intra-insular occasionally peri-insular fibrosis with enlargement of the islets composed predominantly of β cells. These fibrotic and enlarged islets usually were of irregular, bizarre shape and showed a lobulated pattern. A moderate amount of hemociderin was also seen around these islets. (Fig. 1, 2).

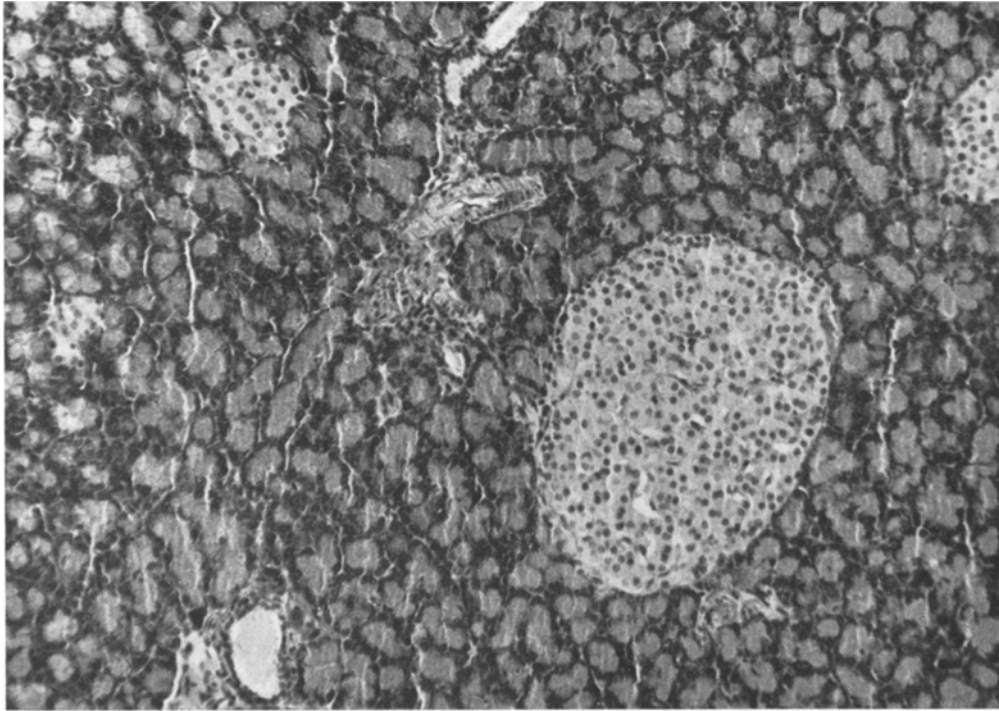


Fig. 1. Islets from an old male rat ("Normal" group). (Hematoxylin-Eosin, $\times 200$)

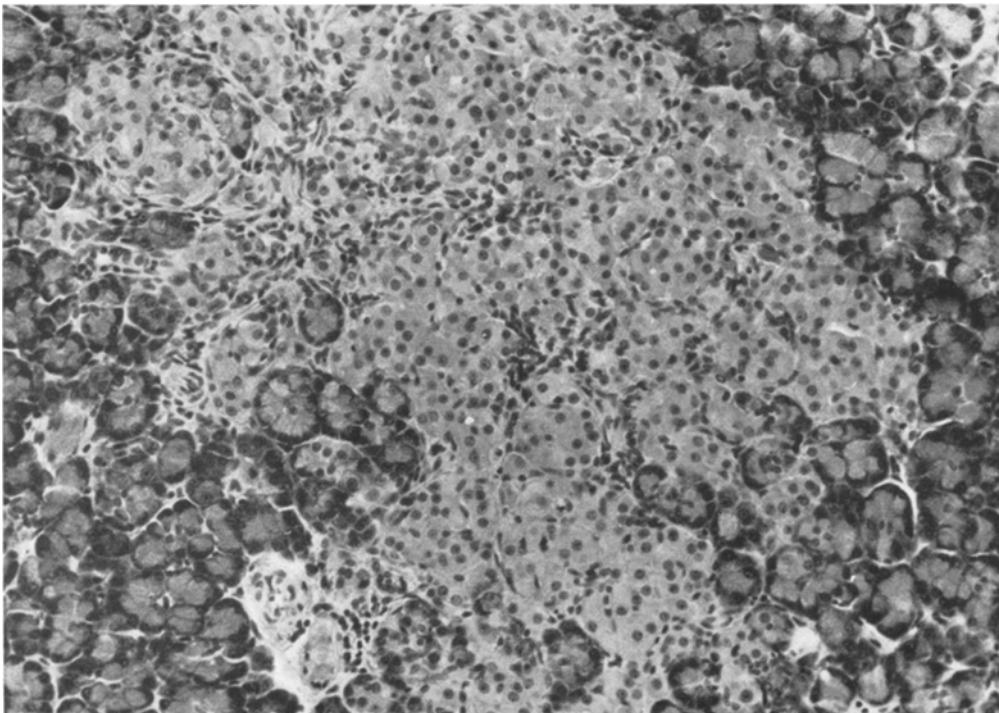


Fig. 2. Islet fibrosis and enlargement in old male rat. (Hematoxylin-Eosin, $\times 200$)

As it is seen from Fig. 3, the tolerance curve of the old rats with no obvious islet change differed markedly from that of healthy young rats. With the exception of 0 and $\frac{1}{2}$ hour blood sugar levels, all the other values were higher (statistically significant) in the old group and the curve exhibited no tendency of returning towards normal. The 5th hour blood sugar was only 24 mg% below the $\frac{1}{2}$ hour level. This abnormal pattern was further exaggerated in old animals with islet fibrosis and enlargement. Here all the points were significantly higher than those of the values of the two other groups and the curve exhibited a definite rise from the second hour. The 5th hour level was 200 mg% and only 4 mg% lower than the $\frac{1}{2}$ hour value.

Discussion

The present study confirmed our previous observation concerning the high incidence of a spontaneous islet fibrosis and enlargement in aging male Sprague-Dawley rats [8]. Similar islet alterations have been produced in the rat by partial pancreatectomy [6] sulfonylurea treatment [7, 1] or a combination of both [10, 4]. These authors suggested that the islet lesion represents a sign of compensatory hyperplasia and

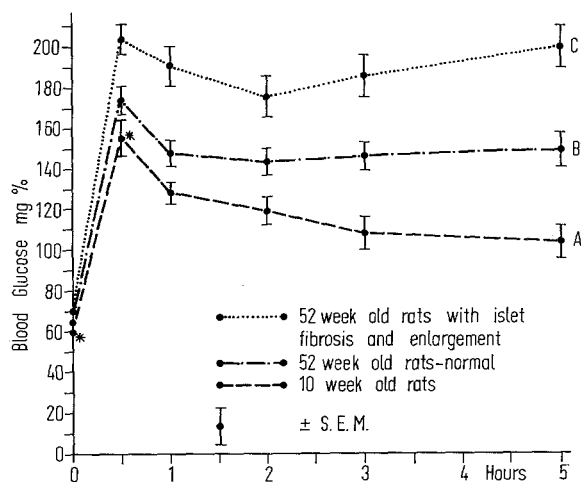


Fig. 3. Compiled glucose tolerance values and standard errors of the mean in the various groups (S.E. is not illustrated at 0 hour. Statistical significance exists between group B and C at 0 hour.). The differences between groups are statistically significant with the exception of values marked with asterisk

could be regarded as an indication of islet hyperfunction. The regeneration, which follows the reduction of islet mass, however, could not be regarded in most cases functionally adequate, since FRIEDMAN and MARBLE [6] found a reduced glucose tolerance in partially pancreatectomized animals. In our functional studies the rats had no fasting hyperglycemia, however, an abnormal (diabetic type) glucose tolerance was disclosed.

A diminished glucose tolerance in elderly humans [12, 2, 9, 11, 14, 5] and in rats [3] is shown to occur. Its pathogenesis, however, has not been fully evaluated as relatively few large scale studies have been carried out in the aged to correlate functional response with islet morphology. Our findings appear to support ZHUKOV'S [14] observation in humans which suggested an important role of intra-insular pericapillary fibrosis as a basis of diminished glucose tolerance.

It is tempting to speculate that in our male rats some unknown factor leads to an increased need for insulin and as CREUTZFELDT and GEGINAT [4] suggested following sulfonylurea treatment to a decreased insulin storage by the beta cells. The ensuing morphological alteration of the islets, manifested as intra-insular fibrosis, in turn results in islet regeneration and enlargement (nodular regeneration). This change would then compensate at least to some extent for the discrepancy between insulin demand and availability.

The fact that the normal old rats (without islet fibrosis) in our experiments also presented lower tolerance indicates that the morphological changes are preceded by functional alteration of the islets. Another explanation is that other factors may also contribute to the abnormalities of carbohydrate metabolism in old animals. Further experiments are in progress to investigate these possibilities.

Acknowledgement. We are grateful to Mr. J. DUBUC and his staff for the blood glucose determinations.

References

- BÄNDER, A., A. HAUSSLER, and J. SCHOLZ: Ergänzende pharmakologische Untersuchungen über Rastinnon. *Dtsch. med. Wschr.* **82**, 1557—1564 (1957).
- CHESROW, E.F., and F.M. BLEYER: The glucose tolerance test on the aged. *Geriatrics* **9**, 276—282 (1954).
- COLE, V.V., and B.K. HARNED: Diabetic traits in a strain of rats. *Endocrinology* **23**, 318—326 (1938).
- CREUTZFELDT, W., and G. GEGINAT: Glucosetoleranz und Inselregeneration bei teilpancreatektomierten Ratten unter ACTH und langfristiger Behandlung mit N-(4-Methyl-benzolsulfonyl)-N'-butylharnstoff. *Arzneimittel-Forsch.* **8**, 464—469 (1958).
- CROCKFORD, P.M., R.J. HARBECK, and R.H. WILLIAMS: Influence on age on intravenous glucose tolerance and serum immunoreactive insulin. *Lancet* **1966 I**, 465—467.
- FRIEDMAN, N.B., and A. MARBLE: Island hyperplasia in the partially depancreatized rat. *Endocrinology* **29**, 577—582 (1941).
- GEPTS, W.: Contribution à l'étude morphologique des îlots de Langerhans au cours du diabète. Les éditions Acta Medica Belgica, Bruxelles, 1957.
- HAJDU, A., and G. RONA: Morphological observations on spontaneous pancreatic islet changes in rats. *Diabetes* **16**, 108—110 (1967).
- JESSOP, W.F.E.: The effect of aging on carbohydrate metabolism. Experimental Research on Aging. Symposium of the Biological and Medical Research Committee of the International Gerontological Association's European Section. Basel, p. 145, 1956.
- LÓUBATIÈRES, A., A. SASSINE, C. FRUTEAU DE LACLOS et P. BOUYARD: Actions des sulfamides hypo-

- glycémiant sur la croissance du rat blanc et l'histologie du pancréas. C.R. Soc. Biol. (Paris) **151**, 957—959 (1957).
11. SILVERSTONE, F.A., M. BRANDFONBRENER, N.W. SHOCK, and M.J. TIENGST: Age differences in the intravenous glucose tolerance tests and the response to insulin. F. Clin. Invest. **36**, 504—514 (1957).
 12. SMITH, L.E., and N.W. SHOCK: Intravenous glucose tolerance tests in aged males. J. Geront. **4**, 27—33 (1949).
 13. WEXLER, B.C., and C.T. FISCHER: Abnormal glucose tolerance in repeatedly bred rats with arteriosclerosis. Nature **200**, 133—136 (1963).
 14. ZHUKOV, N.A.: Part played by age changes in insular apparatus of pancreas in development of diabetes mellitus in middle and old age. Sovetskaya Meditsina **28**, 13 (1964). (Cit. by Fed. Proc. **24**, T 597—T599 (1965).

A. HAJDU
Department of Biology
Ayerst Research Laboratories
1025 Laurentien Blvd.
Montreal, Canada