Neurology in Europe I: D. Bartko, F. Gerstenbrand & P. Turčáni eds. © 1990 John Libbey & Co. Ltd. pp 26-33.

Cerebral stroke and glucose metabolism

D. Bartko, F. Gerstenbrand, M. Žuži, Veronika Vestenická, P. Turčáni

1st Department of Neurology, Comenius University, Research Centre of Cerebrovascular Diseases and Stroke, IMB, Bratislava, Czechoslovakia.

INTRODUCTION

It is known that the changes in glucose metabolism can be one of the risk factors of the onset of cerebral infarction. From literary data, the frequency of such changes is different (Gertler et al. 1976, Jacobson 1967, Kannel 1971, Wolf et al. 1977, Maruyama 1978). From 1736 patients with cerebral infarction Bartko found diabetes mellitus only in 56 cases (Bartko, 1981). There were clinically clear diagnosis of diabetes mellitus and not laboratory verified diagnosis of DM. In the Framingham study, the disorders of glucose tolerance belong to the risk factors of cerebral infarction.

The aim of this study was: 1. to analyse the changes in glucose tolerance in patients with cerebral infarction (CI), 2. to compare these changes with the changes of glucose tolerance in the group of atherosclerotics and hypertonics (AS & VH), quasi potential candidates of cerebral infarction, 3. to correlate these changes with time-course of disease, 4. to assess whether the mechanism of these changes can be due to the peripheral or central disorders of glucose balance.

MATERIAL AND METHODS

Material consists of 189 patients, 118 of them suffered from cerebral infarction, mean age 57.1 years ± 4.6 years, 71 atherosclerotics and hypertonics, mean age 58.1 ± 5.3 years. Control group consists of 94 healthy subjects, mean age 56.8 ± 4.4 years. The diagnosis was confirmed by clinical examination, cerebral serioangiography (Serioangiograph, Philips), electroencephalographic examination (Accutrace 200, Beckman) including EEG power spectra and mapping of electric activity of brain (Pathfinder, Nicolet), battery of biochemical tests of blood serum and CSF, hemorheological examination (blood platelet aggregation, viscosity, coagulation tests), CT examination and by measurement of regional cerebral blood flow by means of clearance method using ^{133}Xe. The degree of neurological deficit was quantified by BI score (Bartko, 1981). Patients included in the study were carefully selected according to exactly defined criteria and all patients with diseases of liver, kidney, glandula thyroidea and GIT were excluded from the study.

Following methods were used:
1. Oral glucose tolerance test (oGTT). The efficacy of this test was increased by double load of glucose administrated at the time of the increase of glycaemia.
2. ACTH test Two or three days after the oGTT another test has been performed, namely i.m. administration of ACTH (25 I.E./sq.m. of body surface) 10 min prior to the administration of glucose (Corticotropin, Organon). It has been assumed, that ACTH may increase the sensitivity oGTT (Berger and Island, 1952). Simultaneously Thorn's test has been performed.
3. Intravenous glucose-tolerance test (i.v. GTT). 25 g of glucose in 50% solution was administered into v. cubiti within 4 min (Bansal et al., 1975). The venous blood was collected at 15th, 25th, 35th, 45th and 55th minute after the administration . Time 0 was set to 2 min after the glucose application. For the calculations following equations were used:

$$G_t = G_0 \cdot e^{-kt}$$

G_t - blood glucose concentration at time t
G_o - blood glucose concentration at time 0
k - rate constant
t - time after administration of glucose

Glucose utilization rate was expressed in utilization coefficient (Amatuzio et al., 1953)

$$K = \frac{2.3\ (\log G_1 - \log G_2}{t_1 - t_2} \cdot 100$$

G_1 - blood glucose at 15th minute
G_2 - blood glucose at 55th minute
t_1 - time in min (15 min)
t_2 - time in min (55 min)

4. Estimation of immunoreactive insulin (IRI). Immunoreactive insulin measured by RIA was used for detection of possible disturbances of glucose metabolism at peripheral level.
5. Pyrifer test. For the evaluation of the function of diencephalohypophyseal system Pyrifer test was used. Pyrifer (25 V, fy Aristopharm) was administrated intravenously and changes in blood pressure, pulse, body temperature, blood glucose and in white cell count were observed.
6. Glycosylated hemoglobin. The glycosylated hemoglobin is a very useful index of glucose control over time in patients with diabetes. It gives the better informations than routine glucose monitoring. It was measured by HPLC.

RESULTS

Oral glucose tolerance test
The patients with CI had significant higher blood glucose concentration as compared to the controls, the levels of blood glucose after simple and double load of glucose were higher, the "peak" of blood glucose was delayed and it failed to attain the starting values (fig. 1). Similar trend, however with less pronounced changes, was observed also in the group of AS and VH. It was found out that these changes

were more apparent in "severe" brain infarction. The dynamic follow-up of these changes showed (after 2 and 4 weeks) a certain improvement in the ability of organism to metabolize glucose, but it was of little significance (fig. 2).

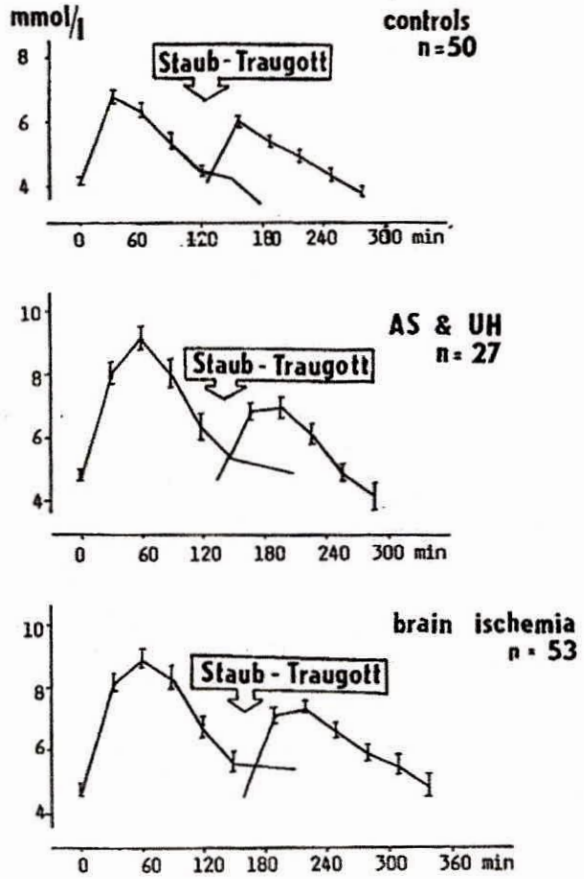

Fig. 1. *Changes in oGTT under simple and double load of glucose in the controls, in the group of AS & VH and in the group of CI.*

oGTT after administration of ACTH

On the figure 3 are given changes in oGTT before and after administration of ACTH. It was found out that after administration of ACTH the glycaemia curve in patients with cerebral infarction is different in comparison to the controls. Expected decrease in eosinophil count was not observed (control group - 72.1%, CI group - 63.3%). Similar trend of changes was observed also in the group of AS & VH, however, the changes were less significant. Thorn's test excluded dysfunction of adrenal gland.

I.v. glucose tolerance test (i.v. GTT)

The changes in i.v. GTT are given in figure 4. It can be seen, that decrease in glucose concentration after intravenous glucose administration is significantly slower in the group of patients with CI as compared to the control group. Similar trend was observed also in group of AS and VH. This observation is in good agreement with results of analysis of glucose tolerance coefficient, which is in the group of CI significantly lower as compared to the controls (tab. 1).Summarising, the changes in glucose tolerance in the group of patients with CI and in the group of AS & VH are not due to the variability of intestine resorption of glucose.

Insulin secretion after glucose load - changes in immunoreactive insulin (IRI)

Disturbances in glucose metabolism accompanying the focal cerebral ischemia can be due to the changes in glucose utilization at the periphery, mainly due to the disorders of insulin production. From this point of view the aim of this part of our study was to analyse the changes in insulin production which is one of the main regulatory factors of glucose balance. The changes in IRI shown delayed but sufficient secretion of insulin (fig. 5). Based on this finding we conclude that decreased glucose tolerance in focal cerebral ischemia is not caused by disturbances of glucose metabolism at the periphery level.

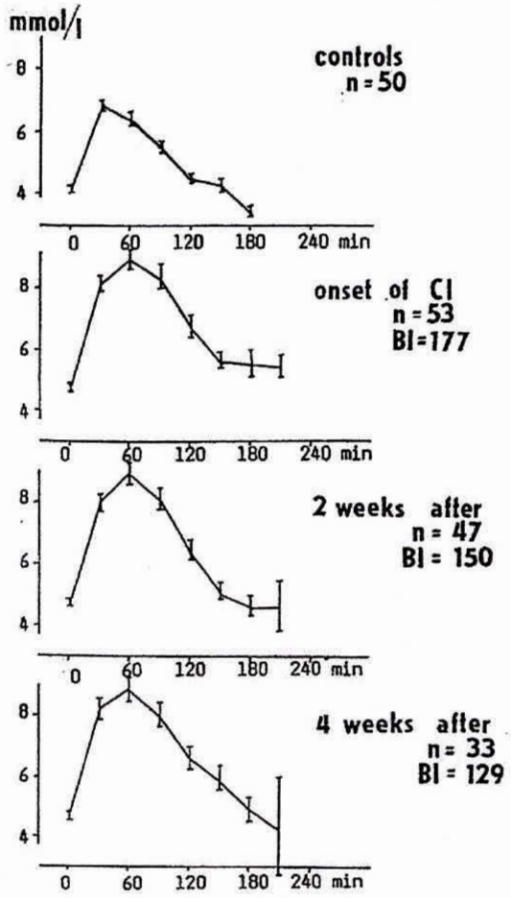

Fig.2. *Changes in oGTT in the group of patients with CI following the onset of disease, 14 and 28 days after the onset of disease in comparison to the control group.*

The changes in glucose metabolism. Disorders of diencephalon?

The mechanism of altered glucose tolerance in focal brain ischemia can be due to the functional disturbances of the regulatory metabolic centres of the brain in focal brain ischemia. Functions of these centres were tested by the i.v. administration of Pyrifer. It was evaluated that after Pyrifer administration the parallel increase of the investigated parameters did not occur (i.e. number of leukocytes, body temperature, pulse, systolic and diastolic blood pressure, blood glucose), the peak values did not reach the levels of control group, their increase was delayed, persisted twice as long as in the controls and did not return to the initial values (Fig. 6). A pathological constellation of responses was recorded in 85.71 % of the cases in comparison to 13.33 % of controls (table 2).

Table 1. Changes in glucose tolerance coefficient

Controls	AS & VH	Cerebral infarction	Significance	
$\bar{x}_1 \pm s_{x1}$	$\bar{x}_2 \pm s_{x2}$	$\bar{x}_3 \pm s_{x3}$		
1.74	1.24	1.06	$\bar{x}_3 : \bar{x}_1$	$p < 0.001$
0.43	0.33	0.29	$\bar{x}_3 : \bar{x}_2$	p = N.S.
			$\bar{x}_2 : \bar{x}_1$	$p < 0.005$

A similar trend of changes was found also in the group of AS & VH although in a lower percentage. The results confirmed the assumption that in the mechanism of reduced glucose tolerance at the periphery an important part is involved by the disturbances of functions of regulatory metabolic centres in diencephalon.

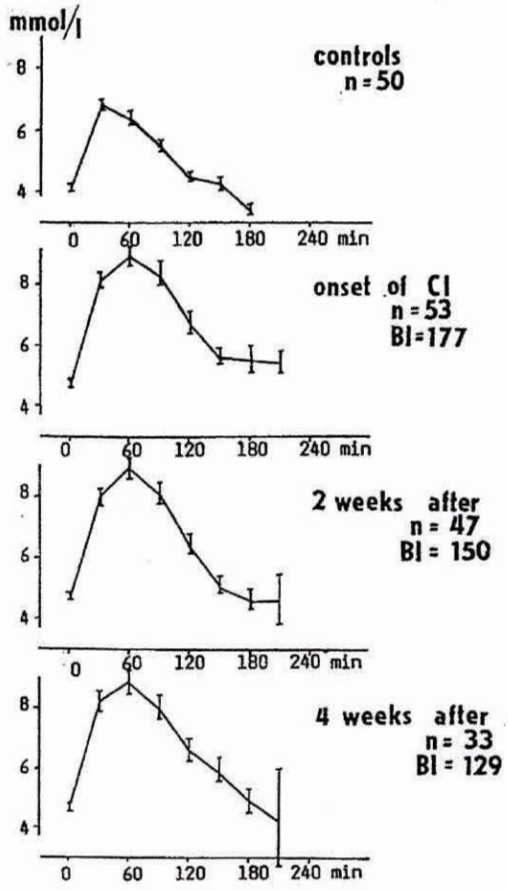

Fig.2. *Changes in oGTT in the group of patients with CI following the onset of disease, 14 and 28 days after the onset of disease in comparison to the control group.*

The changes in glucose metabolism. Disorders of diencephalon?

The mechanism of altered glucose tolerance in focal brain ischemia can be due to the functional disturbances of the regulatory metabolic centres of the brain in focal brain ischemia. Functions of these centres were tested by the i.v. administration of Pyrifer. It was evaluated that after Pyrifer administration the parallel increase of the investigated parameters did not occur (i.e. number of leukocytes, body temperature, pulse, systolic and diastolic blood pressure, blood glucose), the peak values did not reach the levels of control group, their increase was delayed, persisted twice as long as in the controls and did not return to the initial values (Fig. 6). A pathological constellation of responses was recorded in 85.71 % of the cases in comparison to 13.33 % of controls (table 2).

Table 1. Changes in glucose tolerance coefficient

Controls $\bar{x}_1 \pm s_{x1}$	AS & VH $\bar{x}_2 \pm s_{x2}$	Cerebral infarction $\bar{x}_3 \pm s_{x3}$	Significance	
1.74	1.24	1.06	$\bar{x}_3 : \bar{x}_1$	$p < 0.001$
0.43	0.33	0.29	$\bar{x}_3 : \bar{x}_2$	p = N.S.
			$\bar{x}_2 : \bar{x}_1$	$p < 0.005$

A similar trend of changes was found also in the group of AS & VH although in a lower percentage. The results confirmed the assumption that in the mechanism of reduced glucose tolerance at the periphery an important part is involved by the disturbances of functions of regulatory metabolic centres in diencephalon.

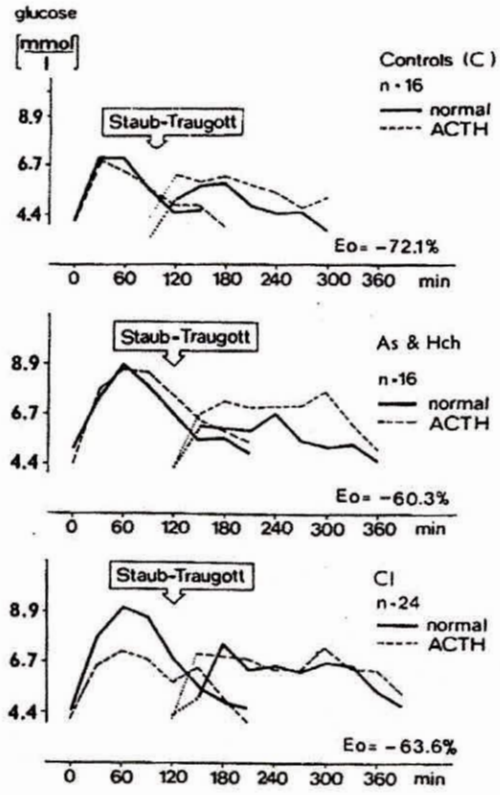

Fig.3. *Effects of ACTH on oGTT in the group of CI in comparison to the controls and to the group of AS & VH.*

Glycosylated hemoglobin (HbA_{1c})
From previous results it was not possible to say if an altered glucose tolerance is really risk factor of CI, because it was observed in both, in cerebral infarction and in the group of AS & VH. It was therefore necessary to find another, more valid marker of disturbed glucose metabolism, which should reflect the changes in glucose tolerance already before the onset of cerebral ischemia, i.e. it was necessary to introduce test which gives the informations about the long-term profile of glucose metabolism. Such parameter is HbA_{1c}. The analysis shown the statistically significant increase of HbA_{1c} in the group of cerebral infarction as compared to the control group. Similar trend was noted also in the group of AS & VH (fig. 7). This was reflected also by the percentage of pathological changes in HbA_{1c}. In patients with CI it represents 49.0% (tab. 3).

Table 2. Pathological changes in diencephalon functions

GROUP	% of pathological changes	Significance	
Controls	13.33		
AS & VH	7.43	0.001	N.S.
Brain ischemia	85.71	0.001	

Table 3. Percentage of increased levels of HBA_{1c} (X + 2Sx)

Controls	0.0%		
AS & VH	42.0%	0.001	N.S.
Brain ischemia	49.0%	0.001	N.S.

Summarising
1. The ability of organism to metabolize glucose in the group of cerebral infarction is decreased. 2. It is decreased also in the group of atherosclerotics and hypertonics, quasi potential candidates

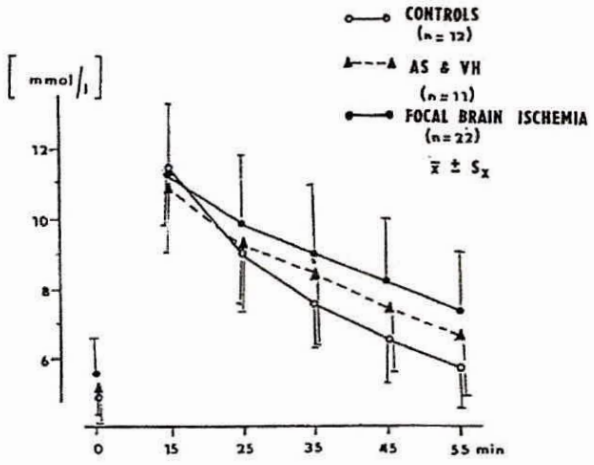

Fig. 4. *I.v. glucose tolerance test in the group of CI in the comparison to the controls and to the group of AS & VH.*

of cerebral infarction. 3. The changes are not due to disturbances of intestine resorption. They were found also after i.v. administration of glucose. 4. These changes are not due to the failure of glucose metabolism at the periphery. Insulin production is preserved. 5. The results confirm that in the mechanism of reduced glucose tolerance at the periphery an important role is played by the disturbances of regulatory metabolic centres in diencephalon. 6. The reduced glucose tolerance is regarded as a risk factor of cerebral infarction. 7. Glycosylated hemoglobin was shown to be a better marker of glucose tolerance tests.

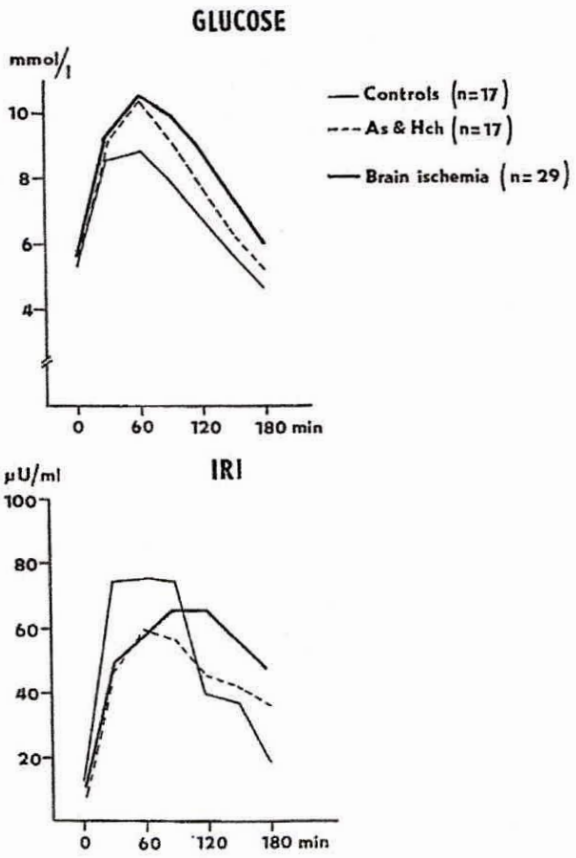

Fig. 5. *The changes in IRI in the group of CI, AS & VH in comparison to the controls.*

DISCUSSION

Numerous epidemiological, clinical and experimental studies revealed a number of factors, which may participate in the pathogenesis of focal cerebral ischemia. One of these factors is also glucose metabolism disturbances. Results of our studies confirmed, that glucose metabolism in focal cerebral ischemia is disturbed. It was reflected by decreased ability of the organism to metabolize glucose, which was tested by examination of tolerance to orally administered glucose. It was shown, that these changes are not influenced by disturbances in intestinal glucose resorption. Similar changes were observed also after intravenous administration of glucose. Glucose tolerance was decreased also in "candidates" for cerebral infarction, i.e. in age-matched patients with atherosclerosis and hypertension.

Interpretation of these results is not simple and is complicated by the fact that glucose metabolism is influenced by several extracere-

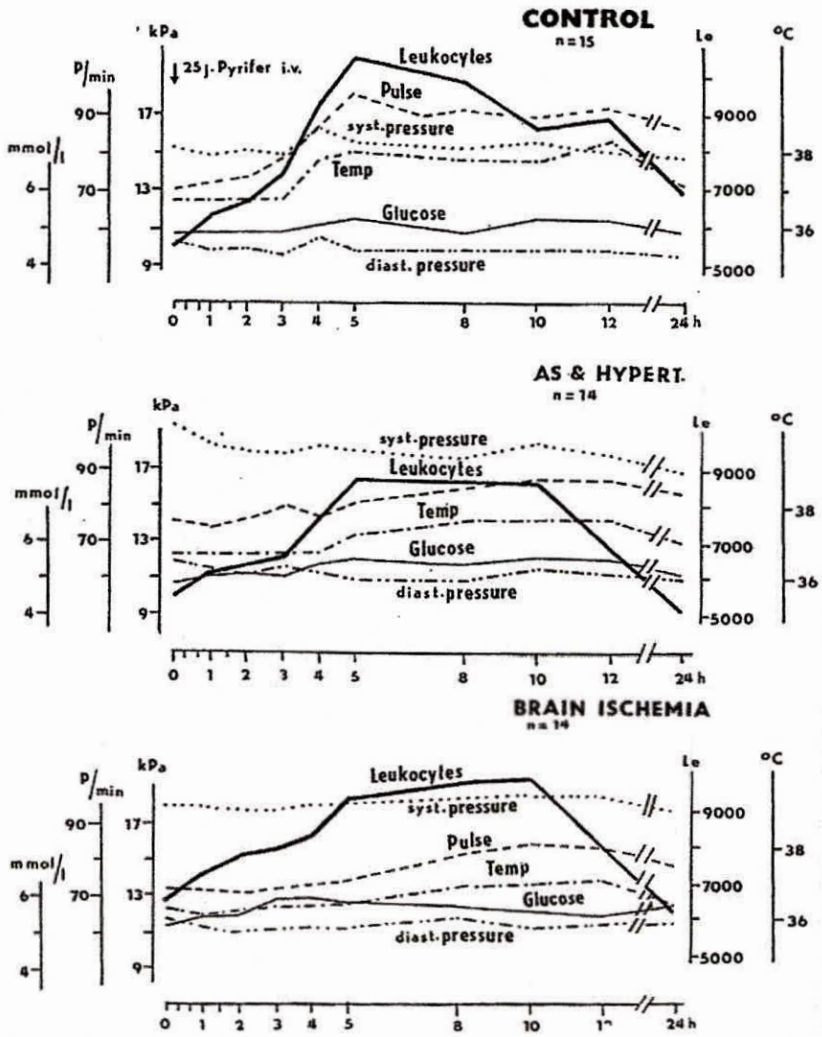

Fig. 6. *The changes in fuction of diencephalon (tested by i.v. administration of Pyrifer) in the group of CI in the comparison to the controls and the group of AS & VH.*

bral factors from glucose resorption in intestine to glucose degradation, by function of pancreas, liver, adrenal gland, thyroid gland and others. Metabolism of glucose is also influenced by function of regulatory metabolic centres. This is supported by many works and it was shown more than 50 years ago by Claude Bernard. He observed hyperglycemia and glycosuria in rabbits after puncture into the bottom of fourth ventricle in the area of calamus scriptorius.

Detailed analysis didn't reveal any disturbances in the peripheral level of insulin secretion. Insulin production was a little delayed but sufficient. This can be interpreted as a consequence of: 1. decreased sensitivity of insulin receptors, 2. the increased levels of

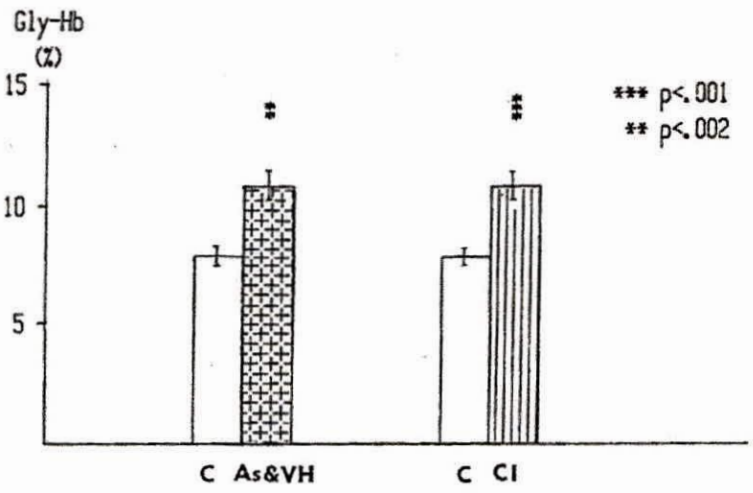

Fig. 7. *The changes in HbA_{1c} in the group of CI in comparison to the controls and the group of AS & VH.*

insulin antagonists, 3. the increase of the insulinase activity, 4. the increased levels of plasma free fatty acids (Gertler et al., 1970, 1976, Randle et al., 1963).

The factor influencing the glucose tolerance is age. Age increasing is accompanied by decrease in glucose tolerance. The highest difference was observed between fourth and fifth decade. We don't have reliable explanation for this results. May be, there is the increased level of insulin antagonists in serum and the decreased sensitivity against insulin of tissues. Taking in consideration our results in the group of AS & VH (age - 60, glucose tolerance decreased), we can't exclude the influence of age. Detailed analysis, however, has shown that glucose tolerance was decreased also in younger patients with CI and therefore, the changes in glucose tolerance is not possible to explain merely by age differences.

REFERENCES

Amatuzio, D.S., Stutzman, F.L., Vanderbild, M.J. and Nesbit, S. (1953): Interpretation of the rapid intravenous glucose tolerance test in normal individuals and in mild diabetes mellitus. J. Clin. Investig. 32, 428 - 436.

Bansal, B.C., Gupta, R.R. and Bansal, M.R. (1975): Serum lipids and uric acid relationship in ischemic thrombotic cerebrovascular disease. Stroke 6, 304 -306.

Bartko, D. (1980): Focal Brain Ischemia. Publ. House, Academy of Sciences, Bratislava

Bousser, M.G. (Paris): Epidemiologie des accidents vasculaires cerebraux. Rev. Med. (Paris) 41, 2213 - 2236.

Gertler, M.M., Leetma, H.E. and Koutroby, R.J. (1976): The assessment of insulin, glucose and lipids in ischemic, thrombotic cerebrovascular disease. Stroke 6, 77 - 84.

Gertler, M.M., Leetma, H.E., Saluste, E., Welsh, J.J., Rusk, H.A., Covalt, D.A. and Rosenberger, J. (1970): Geriatrics 25, 133 - 148.

Jacobson, T. (1967): Glucose tolerance and serum lipids levels in patients with cerebrovascular disease. Acta Med. Scand. 182, 233 - 243.

Kannel,W.B. (1971): Risk factors in stroke due to cerebral infarction. Stroke 4, 423 427.

Maruyama, T. (1978): Clinical studies on the abnormalities of glucose tolerance in acute stage of cerebrovascular disease. Fukuoka Acta Med. 69, 251 - 267.

Randle, P.J., Hales, C.N., Garland, P.B. and Newsholme, E.A. (1963): The glucose fatty acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 13, 785 - 787.

Wolf, P.A., Dawber, T.R., Thomas, H.E., Colton, T. and Kannel, W.B. (1977): Epidemiology of stroke. In: Thomson, R.A and Green, J.R. Advances in Neurology Vol.16, Raven Press, New York

British Library in Cataloguing in Publication Data
European Congress of Neurology (*1st: 1988*)
Neurology in Europe 1.
1. Medicine. Neurology
I. Title II. Bartko, Daniel III. Gerstenbrand, F. IV. Turčáni, P. (Peter)
616.8

ISBN 0 86196 202 8
ISSN 0957 9257

Published by
John Libbey & Company Ltd.,
13 Smiths Yard, Summerley St, London SW18 4HR, UK. +44 (0)81 947 2777
John Libbey Eurotext Ltd.
6 rue Blanche, 92120 Montrouge, France. +33 (1) 47 35 85 52
John Libbey-CIC s.r.l.,
via L. Spallanzani 11, 00161 Rome, Italy. +39 (06) 873054/869810

Printed in Great Britain by Whitstable Litho Ltd., Whitstable, Kent.

NEUROLOGY IN EUROPE I

Proceedings of the 1st European Congress of Neurology
April 1988, Prague, Czechoslovakia

Edited by

Daniel Bartko, Franz Gerstenbrand
and Peter Turčáni

John Libbey
LONDON · PARIS · ROME