

Glucose-Insulin Metabolism In Chronic Schizophrenia

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The pattern of the glucose metabolism in the course of schizophrenia has been widely investigated in the past, mainly as a consequence of the positive psychological results obtained with insulin-coma therapy.

The data in the literature in this regard are frankly contradictory.

A) Hyper- and Hypoglycemia have both been reported, the first in patients with acute onset of the disease, the second in a nosographically mixed group of the subjects.¹

(B) The glucose Tolerance Test has revealed both increased tolerance² and diabetic-like curves, the last being observed in the acute phases of the disease, in the presence of confusion and clouding of the sensorium or severe emotional tension.³

According to Meyer-Gross (1952) and Hennemann et al. (1954), the most peculiar impairment observed in the glycemic curves after glucose load is represented by a lag in the return to the fasting levels, with a deviation in some metabolites, such as an excessive elevation of the lactic, piruvic, citric, and alphaketoglutaric acids and inorganic phosphate.

(C) The Insulin Tolerance Test has revealed an insulin resistance, followed by a prolonged hypoglycemia,⁴ the latter being considered as expression of a failure in the counter-regulating mechanisms, such an exhaustion of the sympathetic-adrenal system, resulting in a lower ability to respond to stress (Farsstaad, 1966).

According to Freeman (1944-46-50-54), P. Lingjaerde (1964) and Shimmelbush (1971), the phenomenon of insulin resistance should not be related to elevated blood levels of catecholamines, glucagon or corticoids, but rather to the presence of an anti-insulin factor, possibly to be placed in the prealbumin fraction of sera, and apparently inhibited by the phenothiazines.⁵

(D) A decreased rate of peripheral utilization of glucose in schizophrenics was suggested by the data of Dobrzanski, et al (1967) and Hayashi (1959).

(E) Variable and contradictory alterations in glucose metabolites and enzymes have been frequently reported.⁶

(F) The free insulin levels, examined as insulin-like activity, are reduced according to Dobrzanski et al.

(1967), suggestive of a decreased ability to split protein-like complexes.

Kallio, et al (1967) reports the presence of hypoinsulinemia, diagnosed indirectly through the tolbutamide test, which apparently occurs only in patients treated with insulin-coma therapy.

Examining the insulin metabolism, through the use of radioactive labelled material, Corsini, et al (1964) observed mostly normal curves, but in some cases they were prolonged, speaking for a delayed removal of insulin from the blood. This phenomenon could be due to the presence of a carrier substance.⁷

(G) The presence of anti-insulin antibodies had always been excluded.⁸

The contradictions in the reported results induced us to examine the problem under the profile of a possible relationship between biochemical impairments and peculiar nosographic or symptomatologic subclassifications of the disease. This was suggested by our previous experiments, which revealed hypothalamo-pituitary-peripheral gland impairments and decreased hypophyseal secretions in hebephrenic patients with onset of the disease at puberty or immediately postpuberty, in contrast with a fairly good normality of the various hormonal axes in paranoid with onset of the disease in adulthood. Moreover, we observed a strict correlation between hormonal disorders and specific symptomatological patterns in the behavioural-instinctual-affective spheres.

We introduced in our investigation a pharmacological parameters using Haloperidol, a Butyrophenone which specifically decreases the permeability of the adrenergic receptors to catecholamines, thus blocking the reuptake and increasing the enzymatic inactivation by O-Methyl-Transferase (Jansen, 1964).

By means of this pharmacological approach we intended to examine the eventual interference of neurotransmitters on the glucose-insulin metabolism, and in the meantime to control the relationship between

¹ Freeman et al. 1946-50; Rigotti 1954; Hennemann et al. 1954; Germano 1960.

² Shattock 1950; Nadeau 1953.

³ Braceland et al. 1945; Meduna et al. 1945-50; Hoskins 1946; Bellak 1948; Baruk 1950; Simon et al. 1951; Puech et al. 1957; Joarosz 1961.

⁴ Meduna et al. 1942-45; Lingjaerde 1953-56; Jarosz 1961; Mueller 1962; Martin 1970; Franzen 1970.

⁵ Walaas et al. 1965; Mueller et al. 1969.

⁶ Hennemann 1954; Altschule 1954-59; Takahashi et al. 1960; Honda 1963; Bowman et al. 1968; O. Lingjaerde 1968.

⁷ Pearson 1959; Yalow 1961.

⁸ Corsini et al. 1964; Dobrzanski et al. 1967; Martin et al. 1970.

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biochemical impairments and psychopathological parameters of the patients.

Material

We examined 18 schizophrenic subjects: 9 females and 9 males, aged 22-62 years, with onset of the disease between 5 and 29 years before our experiments.

The diagnosis of schizophrenia was done according the nosographic criteria of the O.M.S.

They were divided in 10 hebephrenic, with onset of the disease in a pubertal or immediately postpubertal age, and 8 paranoid with onset of the disease in adulthood.

Patients with previous history of cerebropathies, cerebral trauma, organic diseases, overt endocrinopathies and obesity were not introduced in this experiment. They were on the same common hospital diet, and subjected to the same hygienic rules.

None of them had received electroconvulsive or insulin-coma therapy for the previous 3 years. They were off psychotropic drugs at least for 10 days before the beginning of our experiments.

It must be mentioned that they had been previously examined under the profile of the pituitary-gonadal secretions, the hypothalamo-pituitary-adrenal response to stress, and the GH secretion. The hebephrenics displayed the common features of a marked deficiency in the hypothalamo-pituitary secretions and responses to stimuli, with high variability of the GH response to insulin, while paranoid showed fairly normal endocrine parameters.

The controls were represented by 12 healthy, mentally normal, non-hospitalized volunteers: 6 males and 6 females, belonging to the hospital staff, matched for age to the schizophrenic patients, with no psychopathological history in the family.

Methods

The blood glucose and insulin levels were examined through the Glucose Tolerance Test, using a standard oral dose of 100 grams of dextrose, according to the following schedule.

All the patients fasted and rested in bed at least for 12 hours before the experiment and up to the end of it. Blood samples were drawn at 8 a.m., 30' before the dextrose administration, at the moment of the administration, and thereafter at 30' — 60' — 90' — 120', using a cannula inserted in a forearm vein and kept patent by using a saline solution infusion. The blood insulin was analyzed by the radioimmunological assay of Hales and Randle (1963), using a double antibody procedure. The blood glucose was analyzed by a glucose oxidase method. The experiments were done twice at the beginning of the research, at a 48-hour interval before starting any therapy.

Then the patients were treated with Haloperidol, 6 mg. a.d.i.m. for 30 days to a total dose of 180 mg. The

controls received no therapy. During this period the glucose and insulin curves were examined after 10-20-30 days of therapy.

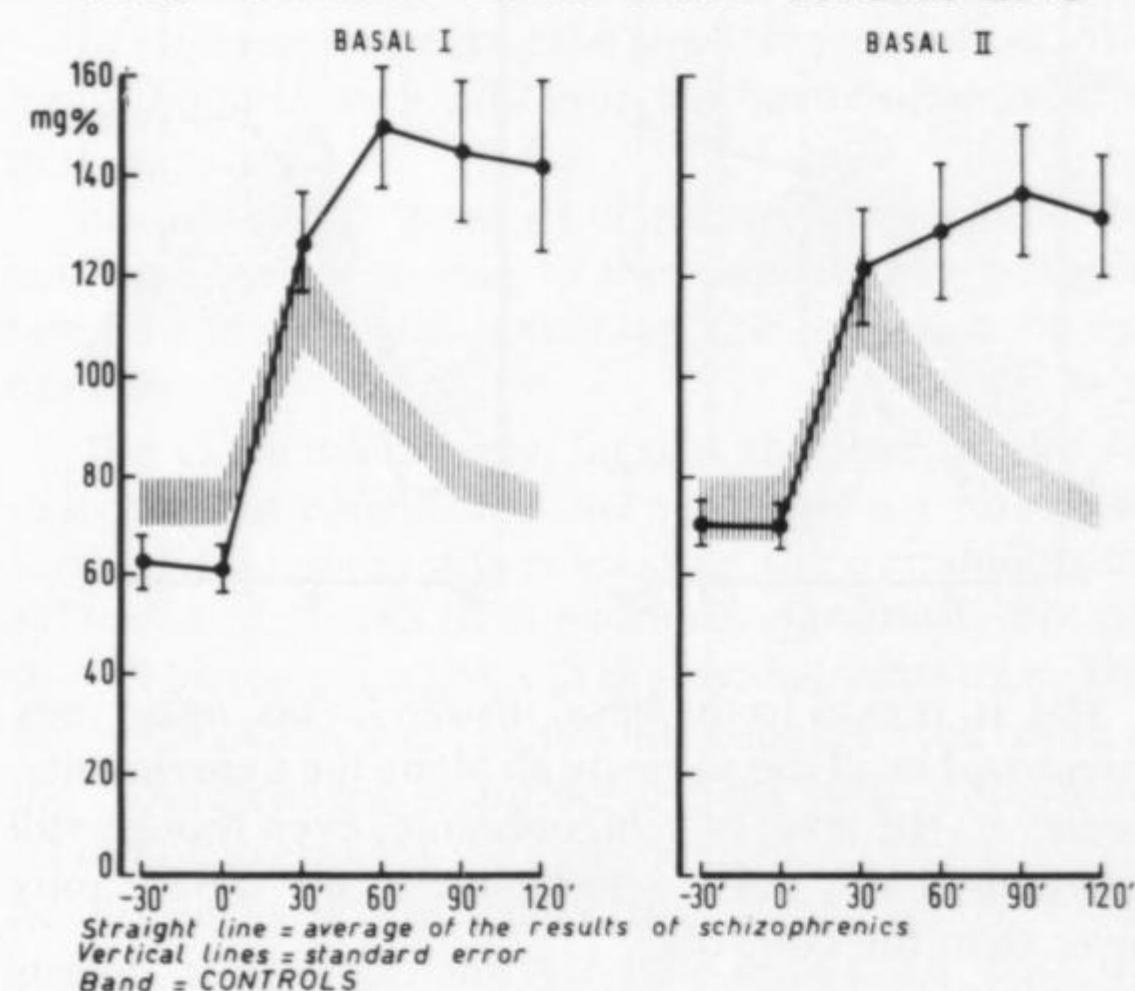
At the end of the experiments, the patients were submitted to a single Insulin Tolerance Test, using O.I. I.U./Kg. body weight of crystalline insulin i.v., controlling the glucose curve at the same time intervals previously reported for the GTT.

The psychological examination was done daily by 3 psychiatrists and by the ward staff. Moreover, the patients were rated with a Wittenborn Rating Scale at the beginning and at the end of the experiments.

Results

The results obtained are reported in the Diagramme I-II-III-IV-V. The significance of the data has been controlled by means of the Student's T, with a P = 0.005.

FIGURE I - GLYCEMIC CURVE UNDER GLUCOSE LOAD

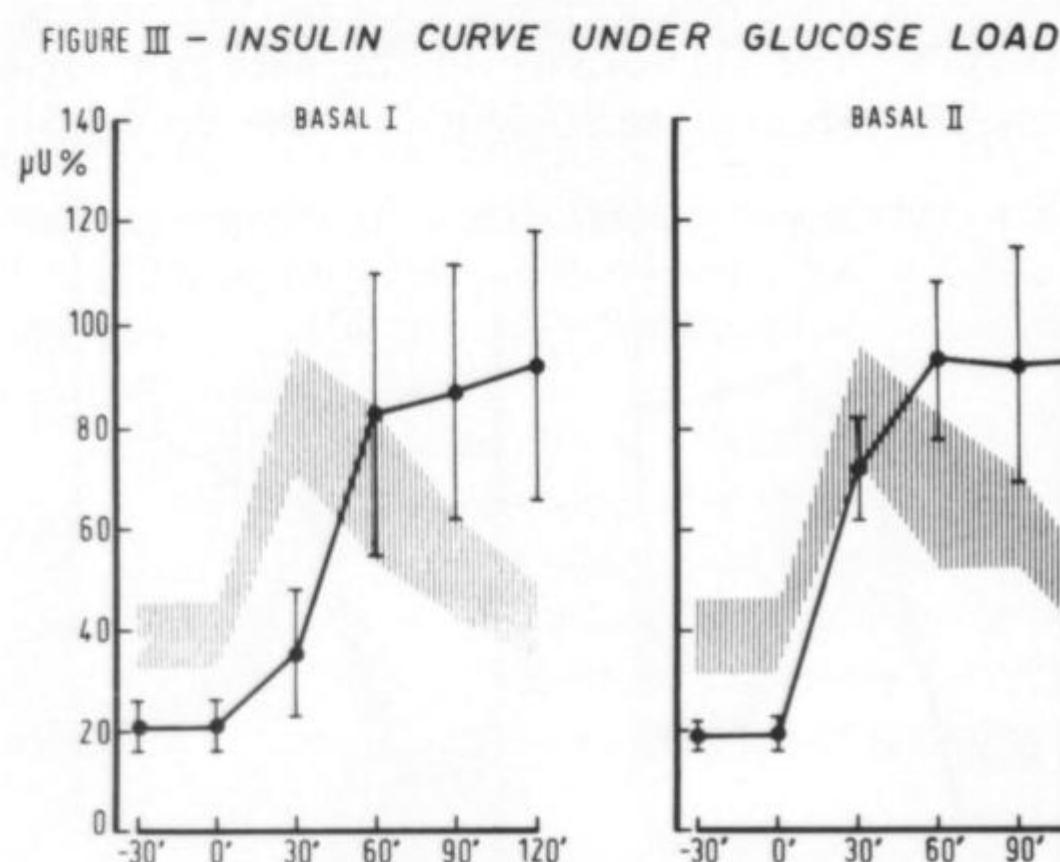
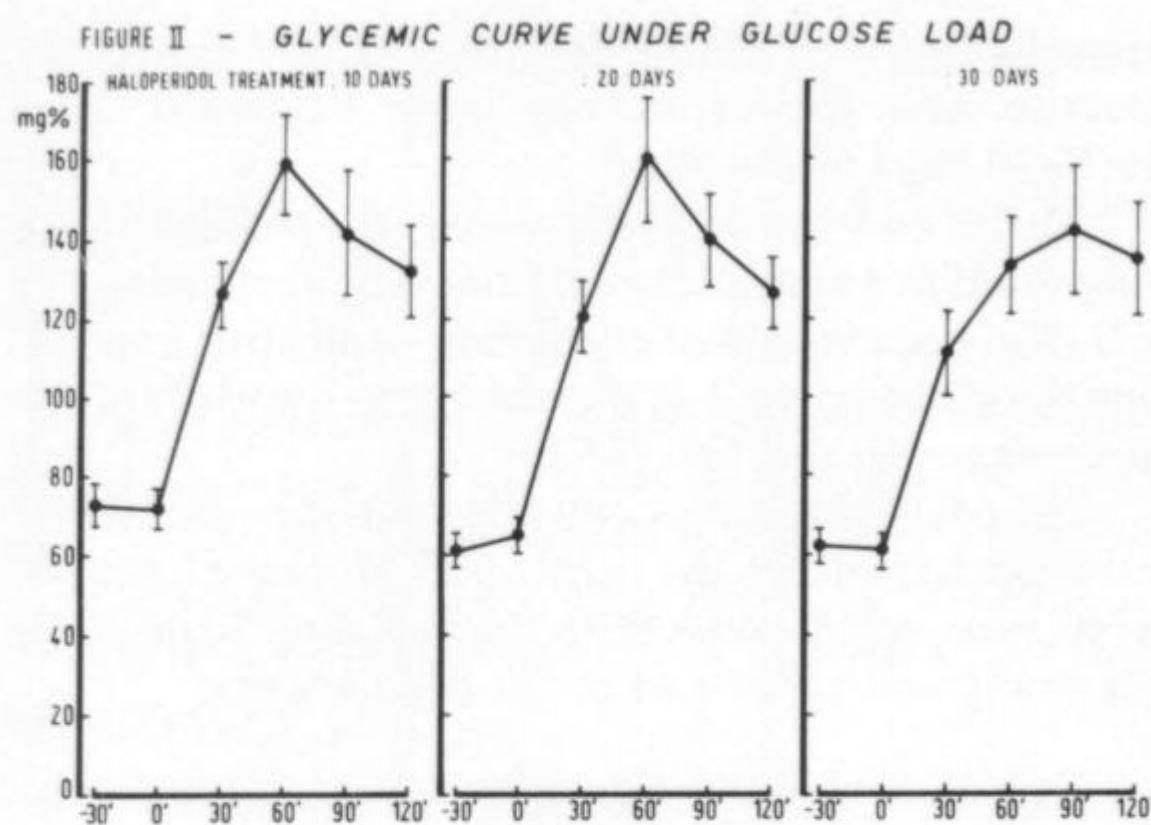


(A) The basal glycemic values are normal in all the patients, as compared to the controls, all along the experiments.

However, under glucose load we observed 3 phenomena:

1. The peak values increased 3-fold in 66% of the subjects before therapy, in 50%, 55% and 73% respectively at 10-20-30 days of Haloperidol treatment. The percentual differences between the five curves are not statistically significant.
2. The glycemic peaks are delayed at 90'-120' in 38% of the subjects before therapy, and in 50%, 27% and 55% at 10-20-30 days of the Haloperidol treatment. Again the percentual differences at the various experimental times are not statistically significant.
3. The glycemic levels at 120' are still frankly higher than the prestimulation ones in 100% of the patients.

Female patients seem to present higher peak values than the males before the therapy, with a statistically significant difference. However, under Haloperidol such a difference disappears.



(B) In regard to the basal insulin levels, again they are normal in all the subjects all along the experiments. However, the level of schizophrenic, even though still included in the normal parameters are significantly lower than the controls.

1. The peaks after glucose display a 4-5 fold increase in 60% of the patients before therapy, in 77%-88% and 83% respectively at 10-20-30 days of the Haloperidol treatment. The percentual differences between the 5 curves are not statistically significant.
2. The peaks occur at 90'-120' in 55% at 10-20-30 days of Haloperidol treatment. The percentual differences are not statistically significant.
3. At 120' the insulin levels are still frankly higher than the prestimulation ones in 100% of the subjects.

No differences were observed between males and females.

(C) The response to the exogenously administered insulin reveals:

1. The nadirs occur always at 30' in all the subjects.
2. The decrement is normal in 88% of the males, with a 22% of subjects displaying severe hypoglycemia. The phenomenon is more evident in the females, where only the 45% is normal and the 55% show severe hypoglycemia. The difference is statistically significant.

FIGURE IV - INSULIN CURVE UNDER GLUCOSE LOAD

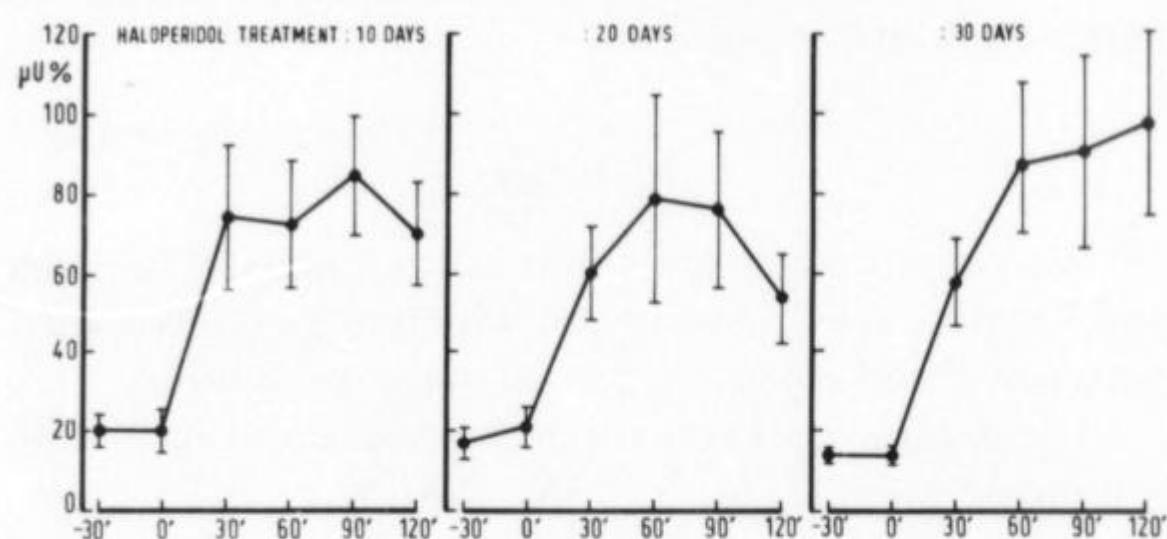
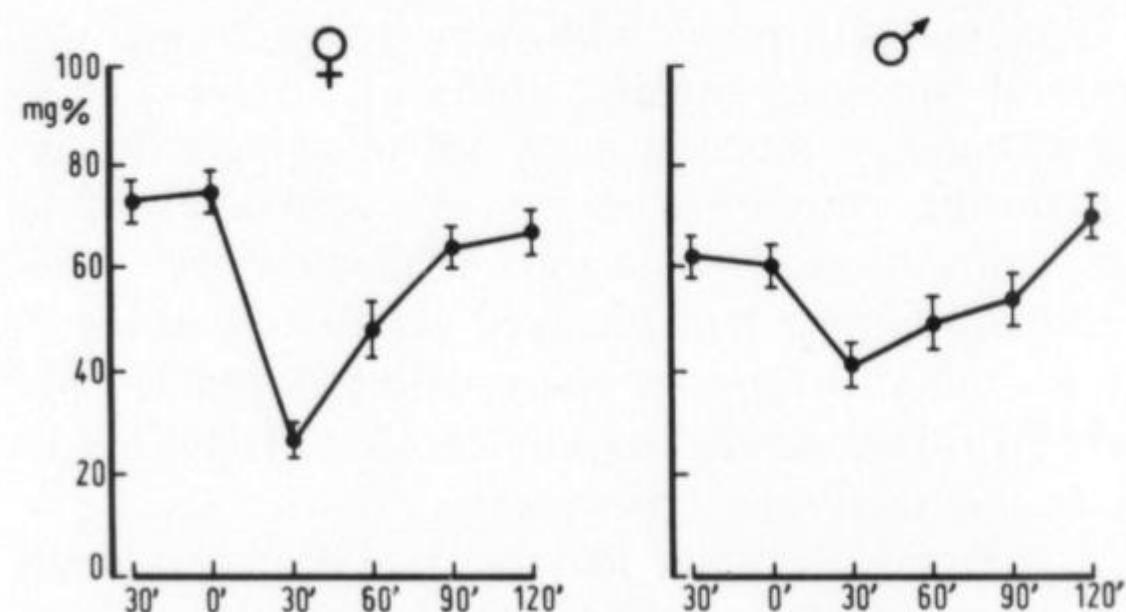


FIGURE V - GLYCEMIC CURVE UNDER INSULIN STIMULUS



3. The return to prestimulation levels occurs normally at 120'. We never observed the phenomenon of prolonged hypoglycemia.

The age of the patients seems to interfere with the severity and frequency of the metabolic impairments. Insulin and glucose peaks are delayed at 90-120' more frequently in patients after the age of 30 years than in younger subjects. The significance of this difference, however, is dubious.

The age of onset of the disease seems also to present a certain relationship with the metabolic derangements. Patients with onset after the age of 30 years seem to present an increased frequency of impairments, represented by delayed peaks at 90'-120'. Again the significance of the datum is dubious.

No differences were observed between paranoid and hebephrenics. Examining the possible relationship between biochemical impairments and psychopathological parameters we observed a significant parallel between the severity of certain symptomatological characters and of the metabolic derangements. They are:

1. Extreme mental deterioration
2. Severe mood flattening
3. Withdrawal from reality and autism
4. Psychomotor excitement, disjointed from reality and devoided of affective contents.

The correlation is highly significant with the insulin derangement and less evident with the glucose impairment.

Discussion and Conclusions

Our data suggest some preliminary considerations.

It is evident that the insulin-glucose levels in basal conditions are normal in our patients. However, the glucose load brings to light a severe metabolic impairment, which, for its characteristics, could be defined as chemical diabetes. In fact it includes:

1. Increased and delayed glucose peak levels, with prolonged hyperglycemia.
2. Increased and delayed insulin peak levels with prolonged hyperinsulinemia.

The response to the exogenously administered insulin is normal versus increased.

As we have observed previously sex and age seem to interfere with the phenomenon. In fact, even though the significance of the data is dubious, females, older patients, and subjects with onset of the disease in late adulthood reveal an increased frequency and severity of pathological data.

The presence of a chemical diabetes, and its eventual correlation with the schizophrenic process, is difficult to be explained. We can exclude the possibility that the phenomenon is causal, as it is present in the 100% of our patients.

The possibility that the previous administration of long-lasting treatments, either electric-shock, insulinoma or psychotropic drugs, could be responsible for the phenomenon is unlikely. In fact, the therapies differed from one subject to the other. Moreover, the data of the literature are not probative for a diabetogenic influence of any of the adopted therapies. Phenothiazines seem to induce hyperglycemia of central origin in experimental animals (Bonaccorsi et al. 1964), but not in men (Landolina et al. 1962; Efron et al. 1966). Electric-shocks induce a very short-lasting hyperglycemia, with immediate spontaneous return to normality (Maiolo et al. 1965). How could we, therefore, connect the schizophrenic process to the observed biochemical impairment?

It is well known that the catecholamines interfere in the insulin metabolism. Noradrenaline and Adrenaline induce a decreased insulin secretion, through an inhibitory activity apparently exerted at the level of the beta-cells of the pancreatic islets (Porte 1966; Werrbach et al., 1970; Toivola et al. 1972; Voyles et al. 1973).

On the other hand, catecholamine impairments have been frequently proposed in the past as basis of the schizophrenic process (Holmberg 1959; Osmond and Smythies 1952-68; Hoffer 1954-57; Leach 1956; Szara 1958; Sourkes 1962; Friedhoff 1962-73; David 1973; Snyder 1973).

Recently, Antelman et al. (1972) and Stein (1972) has introduced the concept that a genetically conditioned excess of 6-hydroxy-dopamine at the level of the Central Nervous System could be responsible for the mental disease. 6-hydroxydopamine is a metabolite which induces irreversible damages of synaptic nerve

terminals resulting in a long-lasting depletion of Noradrenaline.

The consequent lack of the tonic inhibition exerted by the Noradrenaline on the pancreatic beta-cells could be responsible for the increased insulin levels. The impairment seems to be relative, as the increased insulin secretion appears only under stimulus, and not in basic situations. This could be explained by a partial Noradrenaline insufficiency, with an impaired homeostatic mechanism in situations of increased demand. However, another element should be introduced. An increased insulinemia should induce an hypo and not the hyperglycemia observed. The apparent insensitivity to the endogenous insulin displayed by our subjects must be related to a peripheral cause.

We can exclude an ACTH, cortisol or GH hypersecretion, as we previously demonstrated that our patients present phenomena of hypo and not hypersecretion of these axes.

We did not investigate the possible presence of insulin antibodies which, however, has been excluded in the past literature.

Moreover, our patients displayed an excellent versus excessive response to the exogenously administered insulin, which excludes the presence of antibodies.

We could tentatively suggest that the insulin secreted by our patients is either a proinsulin or an altered form of hormone, still possessing the immunological properties detected by the radioimmunoassay but not the full biological activity of the normal substance. This secretion of abnormal metabolites could be the result of the Noradrenaline insufficiency: the lack of the tonic inhibition exerted by the catecholamine on the pancreatic beta-cells would induce the spilling in the blood stream of elements not yet fully active. Or else, the insulin could be linked to a carrier substance inactivating the hormone and in the meantime reducing its removal from the blood, as suggested by Corsini (1964). And we can mention also the hypothesis of Walaas (1965) and Mueller (1969) on the presence of an anti-insulin factor related to the prealbumin fraction of sera. The treatment with Haloperidol does not seem to modify significantly the biochemical derangement. If we consider that the Haloperidol reduces the catecholamine levels in the Central Nervous System, and, according to the previously reported hypothesis the Noradrenaline is already reduced in schizophrenics, we obviously can not expect a modification of the observed hormonal impairments.

To establish a connection between specific psychic symptomatologies and biochemical damages seems rather difficult in our patients. In fact, we have observed that the most severe glucose-insulin alterations go in parallel constantly with the presence of deep mental deterioration, mood flattening, withdrawal from reality and autism. This datum suggests that only the long-deteriorating processuality of the disease corre-

lates with the metabolic impairment. That is why hebephrenic and paranoid both present the same endocrine alterations. In fact, if at the beginning of the disease it was possible to clearly differentiate them under the profile of symptomatology and kind of processuality, when we examined them after a long history of chronicity, they were sharing the same characters of mental deterioration and mood flattening.

In conclusion, we can suggest that the impaired glucose-insulin metabolism is related in our patients only to the deep deteriorating processuality of the mental disease. We can suggest also that the same metabolic derangement is probably responsible for both the mental disease and the endocrine alteration.

Summary

The present study deals with possible connections between the schizophrenic syndrome and alterations of the glucose-insulin metabolism. Data have been obtained in 18 patients, 9 males and 9 females, aged 22-62 years, suffering from chronic schizophrenia of 5-29 years duration. The patients were treated with Haloperidol for 30 days, 6 mg. i.m.p.d. to a total dose of 180 mg.

The glucose metabolism was examined through a GTT (with a glucose load of 100 gr. per os), and an Insulin Tolerance Test (with 0.1 U/kg body weight). The insulin levels were examined under glucose load by the radioimmunological assay of Hales and Randle. The glycemic levels were examined under glucose load by an oxidative method. The psychopathological features were controlled by a Wittenborn Rating Scale.

The metabolic and psychological examinations were done twice before the beginning of the therapy, at 48 hrs. interval, then at 10-20-30 days of therapy.

The results are probative for the presence of a chemical diabetes in a significantly high percent of patients.

The significance of possible neurotransmitter impairments acting at both the biochemical and psychological levels is discussed.

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