# Physiological and Biochemical Changes in Impaired Sugar Metabolism

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**Insulin and Glucagon**

The body's energy requirements are met by the breakdown of glucose in the individual cells.

Several factors are involved in glucose metabolism. These are: insulin, glucagon, the growth hormone, the adrenocortical hormones. Other factors which are involved are the absorptive mechanisms of the gut, which are dependent upon certain enzymes, and its utilization within the body, which again is enzyme dependent.

Not only does insulin play a part in sugar metabolism, but it also plays a vital role in the handling of fats and protein, and recent work has shown that cell multiplication and growth (for instance of the white blood cells and the production of antibodies) is also connected with insulin.

It would seem apparent from recent work that, for its proper physiological function, insulin requires the presence of both chromium and zinc in optimal proportions. Mertz and Schwartz showed that, in the experimental laboratory animal, chromium was essential for normal insulin function, whilst Schroeder has shown that chromium deficiency in rats renders them susceptible to disorders characteristic of diabetes mellitus in man, while feeding them with chromium reversed these changes provided it was done early enough in the development of the disorder.

The Federal Bulletin Report wrote about the Children's Hospital in Jerusalem, in April, 1966, in which the interesting observation was made that children suffering from impaired glucose metabolism, which was not responsive to any other regime, responded overnight when given chromium.

It is interesting to note that Dr. Michael Hambidge, in 1972, reported to the Federation of American Societies for Experimental Biology that the majority of elderly residents of the U.S.A. have impaired glucose-tolerance tests, as demonstrated in clinical trials, and that some 50 percent of these patients with an impaired glucose-tolerance test had their curve restored to normal when given daily doses of 150 micrograms of trivalent chromium.

Again, Schroeder in 1966 reported in the **Journal of Nutrition** that in chromium deficient rats the development of a diabetes-mellitus-like disorder occurred

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and the postmortem findings on these rats showed that there was significant atheromous plaque development by comparison to the postmortem findings upon control groups of rats given daily supplemental trivalent chromium.

He also pointed out that the chromium-fed rats grew faster and reached greater maturity size. They were also much less susceptible to infection, and in this way it seems apparent that the story of chromium parallels that of the other element which I would briefly like to mention to you, namely zinc, which is also essential for normal growth and sexual maturation.

Dr. Sharon Elias and Milos Chvapil in the **Journal of Surgical Research,** in 1973, reported a high level of supplemental zinc is conducive to resilience to the traumata of daily living and showed that it appeared to protect against certain diseases (such as infectious diseases) and to the speed of the rate of wound healing.

Dr. Gordus of Michigan, reporting at the 165th national meeting of the American Chemical Society, in May, 1973, showed that both a high zinc and copper content of hair correlated well with high scholastic achievement, whilst the reverse was true for students at the opposite end of the gradepoint spectrum.

The American Naval Research Unit, reporting in the **American Journal of Clinical Nutrition** in 1966 on the studies of zinc levels in pygmies in the Nile Valley, reported that zinc levels and blood enzyme activities were present in male subjects who in addition to retarded growth also were retarded in sexual development.

Dr. Pedro Cuatrecasas has shown that the traditional concept of insulin function in sugar metabolism is only half of the insulin story. He points out that a much older function is probably that of controlling the body's growth potential; this has been suspected for some time, and several authorities have postulated that insulin, together with growth-stimulating hormones and thyroxin, is essential for the normal growth and maturation of the normal animal. (We must remember the significance of chromium, zinc, and copper in regard to not only optimum growth and sexual maturation, but also in the evolution of intellectual function.)

He pointed out that it may be that early in life, with increased demands for growth, there are more receptors than are apparent in later life, postulating that some of these receptor sites become masked with age. In this way, one can see that the growth and maturation function of insulin therefore loses its importance as the animal ages, and ultimately the sugar-metabolizing function begins to assume dominance.

The evidence for this hypothesis is suggested by the fall in cyclic A.M.P. (cyclic 3'5' - adenosine monophosphate) in cells in the presence of insulin. Further, this fall in the cyclic A.M.P. levels combined with certain other intracellular biochemical events acts as a "signal" for cell multiplication. Lymphocytes and cells of the white-cell series, as already mentioned, have no insulin receptors in their quiescent stage. However, when there is an antigen challenge to the body, masked receptors on the lymphocyte are uncovered, and the inference is that this is a prerequisite for multiplication of this series of cells. Of course, one must note here the susceptibility of diabetics to infection or the worsening of the diabetic state during infection. It is of interest/which I won't go into fully here, that vitamin C and vitamin A have been inculcated in the development of white cells and the immune response. The former has been shown to be essential to white cell growth, and more recent work in Florida has shown that in some way vitamin A increases the immunoresponsiveness in rats inoculated with carcinoma.

In 1968, Mertz reported to the annual meeting of the American Association for the Advancement of Science that chromium participates in binding insulin to the cells' insulin receptors. He pointed out that one of the ways in which the

action of insulin may be diminished is therefore by chromium deficiency.

**Chromium**

It is significant that at birth humans have a higher chromium level than at any other time in their life. Perhaps this is due, in part, to some as yet unknown but normal physiological process, but no doubt dietary considerations play an important part. There can be no doubt that refined foods are deficient in chromium, and in fact **Medical World News** in 1972 reported that in the so-called civilized nations of the world the large groups of elderly people who were tested were shown to have lower tissue concentration of chromium than in similar groups of people from underdeveloped countries.

In **Nutrition News,** of December, 1966, Mertz pointed out that the chromium concentration of the average diet was 50 to 100 parts per billion. It is interesting that he also remarked that this is exactly within the range which, experimentally, leads to chromium-deficient states in rats. Yes, even a rat requires 1,000 parts per billion! We cannot calculate on a weight-for-weight basis—between animals of different species—but we can at least predict that we need at least 10 times more chromium from our diet than we are actually getting.

**The Glucose-Tolerance Curve**

It is not my intention to go into the matter of the normal or abnormal glucose-tolerance curve, as I feel that other speakers today will be going into this aspect. However, I would now like to give a short summary of those factors which we know can affect the glucose-tolerance curve, similar to that found in diabetes.

1) Pyridoxine deficiency
2) The steroids
3) Oral contraceptives

It would seem that we should add to this list chromium and zinc deficiency. Now, just a word about oral hypoglycemic agents. Personally, I think that these agents are among the most dangerous of any medications currently in use, and rather than investigate the dangers of any high doses of vitamins the medical profession should rather be more concerned about the abuse of these agents.

The University Group Diabetes Program, reported in **Medical Tribune** of September, 1971, showed that indeed oral hypoglycemics were effective in lowering the blood sugar, but pointed out that there were more deaths from cardiovascular disorders in this group than among those patients who were managed with insulin and diet, or diet alone. It was suggested that there is an altered fat transport which is a fundamental part of the diabetic process, rather than merely a complication arising from diabetes mellitus.

Before I continue with this aspect of insulin function, I should like to report on John Yudkin's report in **Lancet** of July, 1964, in which he made a comparison of atherosclerotic patients, or those suffering coronary thrombosis, with normal groups from similar background and the same age group. In every single case, the patients were shown to be consuming twice as much sugar as those with normal hearts and arteries.

**Metabolism of Carbohydrates**

After ingestion, carbohydrates are broken down to glucose which (after absorption into the bloodstream) may be: 1) utilized directly as an energy source; 2) directed into the glycogen depots as a reserve fuel supply; or 3) channeled into the fat depots.

That the third route is of prime importance I shall make clear to you (I hope) later in this talk and would remind you at this point of the University Croup Diabetes Program in which it was suggested there is an altered transport which is a fundamental part of the diabetic process.

The normal functioning of nervous tissue is entirely dependent upon the level of blood sugar. Although small stores of glycogen are present in nervous tissue, from the present state of our

knowledge it would seem that this is not used as a fuel. Under normal circumstances, the Respiratory Quotient (R.Q.) of the brain is about one, indicating that the energy source is derived entirely from carbohydrates. However, in starvation it has been shown that the R.Q. of the brain falls to levels lower than 0.7, this being due to the fact that during starvation the brain must derive its energy via the conversion of protein and keto acids, notably beta-hydroxybutyric acid to carbohydrate.

It is obvious, therefore, that while it has been demonstrated that there is no expenditure of energy measurable during the process of cerebration, the demand of the brain for fuel is of overriding physiological importance.

It is also of great interest, in what I have already said earlier in this talk, that as yet receptor sites have not been found for insulin on the cells of the central nervous system. Nevertheless, the overriding demands of the central nervous system for glucose is of paramount importance. This, I postulate, would support the inference that the receptor sites are concerned with cell growth rather than the energy requirement of the cell.

**Glycogen**

Whilst carbohydrates provide immediate needs for the body's energy requirement, it is being shown that considerable amounts of this substance are in fact converted to fat.

Where the utilizable carbohydrate has been used up, then glycogen becomes available as an energy source, undergoing anaerobic breakdown to form lactate which, in the presence of oxygen, is oxidized causing release of energy. Unused lactate is returned to the liver, to re-enter the liver glycogen store via the Cori cycle. Again, the importance of ascorbic acid (this amazing vitamin) may be illustrated by interesting work performed by Swahmi et al., who showed that perfusion of exercised rat muscle by ascorbic acid reduced fatigue. Since we have always considered that fatigue in muscle is due to a build up«of waste product (notably lactic acid) it would be an interesting and, I believe, as yet unperformed experiment to study the effect of ascorbic acid in high doses on those athletes who are engaged in such activities as marathon races, long-distance running, etc.

**Fat**

It has long been known that excess glucose is converted into fat. It has been shown that the free fatty acid turnover is more rapid than had been suspected. For this reason, I would propose that the major pathway by which glucose is able to provide energy to the tissues of the body is by the third path which I mentioned earlier--that is, by the channeling of ingested carbohydrate into the fat depots.

**Metabolic Considerations**

Randall suggested in 1965 that there is a glucose fatty acid cycle which regulates the proportions of the fuels available.

For the first few hours after a meal, the more ready availability of glucose favors the formation of acetyl coenzyme A from pyruvic acid, under the influence of coenzyme A. Continued metabolism of glucose leads to the formation of glycerol phosphate, causing conversion of fatty acid coenzyme A into triglyceride, thus setting the ceiling upon the use of glycerol. If Randall et al. are correct in their proposition, the scheme which they suggest provides a peripheral regulatory mechanism, independent of hormone - mediated central control.

**Glucose**

Glucose is absorbed as fructose after hydrolysis in the small intestine. It is conveyed to the liver where, under the influence of the enzyme fructokinase, D-fructose-1-phosphate is formed, and then the trioses dihydroxyacetone phosphate and glyceraldehyde. That the metabolism of fructose is dependent on insulin is the basis for the usefulness of this sugar, not only in diabetes, but also

in hypoglycemia. Under the influence of lactase, lactose is absorbed as galactose and is introduced into glycogen synthesis and then the other glucose derivatives.

**The Disaccharidases**

These are maltase, invertase (or sucrase), and lactase, which are found in the intestinal juice. Lactase deficiency leads, of course, to milk sensitivity. The congenital absence of the enzyme fructokinase in the liver leads to fructose intolerance. The deficiency of galactose-1-phosphate uridyl transferase, the enzyme which is required for conversion of galactose to glucose, leads to a condition known as galactosemia, a rare defect in which the infant cannot tolerate milk. Unless recognized early, and the infant fed on a galactose-free diet, death rapidly ensues.

**Fructosuria**

This is due to a deficiency of D-fructose-1-phosphate aldolase. In this condition, after ingestion of fructose, the patient is afflicted by severe vomiting and the insidious development of jaundice. For this reason, therefore, sucrose (from which fructose is formed) must be carefully eliminated from the diet. Failure to thrive in an infant fed on artificial milk should cause one to investigate the possibility of a metabolic disease being present.

I will not go into the glycogen-storage diseases, nor will I mention pentosuria, which is of academic interest.

**Blood Glucose Equilibrium**

Except in the case of diabetes mellitus and hypoglycemia, the level of glucose in the blood is intricately balanced in the normal individual. In the fasting state, once the utilizable blood glucose has been used and the glycogen store of the liver depleted, then glycogen is manufactured from the straight chain amino acids derived from protein, in the process of gluconeogenesis. Whilst insulin decreases the level of blood glucose, glucagon increases the level of blood glucose. This is an elegant example of a biochemical homeostatic mechanism. However, recent work has shown that glucagon is rather more than an insulin antagonist. Adrenalin may be of importance in glucose metabolism under certain circumstances, causing as it does a rapid although transitory rise in blood glucose.

Cortisol and the other adrenocortical hormones cause a slow but sustained elevation of blood glucose owing to their effect on the liver, which they stimulate in gluconeogenesis. This function has long been considered to be of prime importance by the followers of Searle Harris and John Tintera in their theory of hypoadrenocorticism.

Growth hormone and thyroid hormone also have an effect as insulin antagonists by a mechanism which is as yet unknown.

**Absorptive Mechanisms**

The absorptive mechanisms already outlined have revealed that an enzyme deficiency disorder may arise due to enzyme deficiency in the gut. But this is not the whole story, for there may be enzyme deficiency at other points in the metabolic chain, as already outlined.

It is surprising to find a large number of patients who have a history of obvious childhood sugar idiosyncrasies, whether previously labeled milk allergies or some other misnomer, who later in life take once again to the food which as infants they were unable to thrive upon. For this reason, I think it is important that we should delve into the pediatric history of each of our patients, and I feel that this idea is corroborated by the newly emerging field of brain allergy. Metabolic disorders, although commonly arising through enzyme deficiencies in the gut, do not end there. Once inside the body, sugars are once again under the influence of their several enzyme systems, a defect in any of which may lead to disease which may be readily recognizable or, I am afraid, all too frequently go undiagnosed. I think that an important message which Orthomolecular physicians

(or any other physicians) should attempt to get across to the public is that "once enzyme deficient, always enzyme deficient."

Again we need not limit ourselves to defects in enzyme systems, for if one considers the number of hormones which are involved in homeostasis within the body, then even further vistas of potential ill health are open to us. Abnormal structures, or deficiency of insulin, glucagon, Cortisol, adrenalin, growth hormone, may all exert their effect to a greater or lesser degree.

When we consider absorption by the cell, we are not considering the simple matter of diffusion across a cell membrane, but an active physiobio-chemical process. Once again, any change in the enzyme systems responsible for the absorption of nutrilites, or the sugars across cell membranes, presents a potential weak link in the chain. The state of health of the cell itself, regardless of functionally deficient enzyme systems, is also of vital * importance. Here we must consider the ionic composition of the cells and the structure and integrity of the cell membrane. Finally, we must take into account exposure of the organisms to various toxins which abound in our environment, which pervert the function of cells at all levels from the simplest tissue cell to the cell of the central nervous system.

When confronted with such a plethora of possibilities in any clinical situation, one must (I believe) retire a few paces and look at the problems from a greater distance. In fact, I think that so far as I am concerned, one should go right back to fundamental considerations. As far as Orthomolecular medicine is concerned, these are that the right molecules should be present in the right proportion, in the right combination, in the right place, at the right time.

While, therefore, standing immediately in front of the problem, we cannot possibly see all the possible reactions and inter-reactions of those processes which we are considering, if we stand far enough back and look at them one by one we can establish (as far as is possible with present methods) that the various components are themselves not in a state of "disorder."

In order to do this, one must think in orthodox medical terms, the way that we have all been trained to think, and to correlate them with the terms of the "new medicine," the knowledge of which we have all acquired. We should, therefore, be looking at the fate of the protein balance and the amino acids. We should be looking at the essential elements. We should be looking at the vitamins, and we should also be looking for those substances which are probably there and which ought not to be there.

In short, what we must do is to build a new kind of pharmacology, as well as a new medicine. We must be well aware, for instance, of the symptoms of relative potassium deficiency, calcium, magnesium, zinc, or chromium deficiency. For many years, we have been thinking in terms of relative vitamin deficiency, and we should now increase our repertoire of vitamins which we know to cover those vitamins which we have not yet considered. We must be prepared to take a fresh look at the amino acids, and we must bear in mind that what is one man's meat is another man's poison; for while one individual can handle certain amino acids normally, another individual may be completely incapable of doing so. We must be prepared to match up in our mind the relationship between amino acids and the vitamins, such as has been done already with Pyridoxine and tryptophan.

I can almost visualize a day when we will be subdividing Orthomolecular medicine yet again and forming a branch of study which might be called "micro-molecular medicine," as we study the individual components of the vitamin molecules themselves—as, for example, the B12 molecule and cobalt.

The title of this presentation was, I feel, rather pretentious (that is, "The Physiological and Biochemical Changes in Impaired Sugar Metabolism"). Such a

presentation would take many hours to cover fully, and I have passed all too briefly, and none too well, over only a few aspects of the metabolism of sugars. So far as the physiological changes are concerned, these are so intimately linked with the pathological changes which I have already mentioned, in regard to a few of the metabolic deficiencies, that to go into them further would be an affront to your medical knowledge. However, once again, it is my feeling that physiological changes have been in process for many years before pathological changes take place. Unfortunately, in medicine we are lucky if we recognize those three conditions — health, predisease, and overt disease. Yet, in Orthomolecular medicine, this should be one of our first thoughts. There can be no doubt that, properly applied, Orthomolecular or nutritional methods could reduce the disease state by some 50 percent in the civilized world.

The secret is to know not only to whom disease is going to happen, but to whom what disease is going to happen, and where that disease is likely to happen—that is, which part of the body is likely to break down. This may seem to be an impossible task to ask of any physician. However, it is my contention that the means are already at our disposal. We are well acquainted with the vitamin B3-deficiency syndrome, and I am convinced that Orthomolecular physicians, generally, easily recognize this before overt disease occurs. Glen Green's work on perceptual disabilities in children, and the work of Cott in this area, has provided us with a fine set of diagnostic pointers which would lead us to a diagnosis before the diagnosis is suspected by the practitioner not acquainted with these methods. The work of Pfeiffer on the trace elements is yet another predisease diagnostic indicator. Marion Seelig has written several papers indicating magnesium-deficiency syndromes which could easily be identified by Orthomolecular physicians. Carl Reich has identified a vitamin D-deficiency syndrome. All of these deficiency disorders can be identified, oftentimes many years before overt symptoms arise.

To summarize, the biochemistry of impaired sugar metabolism is readily identifiable in its most overt form in infants. Unfortunately, this tends to become minimized and overlooked as the child reaches his school years because we expect him to "grow out of his allergies."

The biochemistry of impaired sugar metabolism is, therefore, not simply a matter of deciding who is or who is not hypoglycemic, but who is or who is not sensitive to galactose, to fructose, lactose, sucrose, etc. It may well be that we shall discover in time that the glucose pathway into the fatty acid cycle is disrupted in those individuals who are to become obese, and indeed it is not altogether a surprising finding that many (if not most) of these individuals tend early to be hypoglycemic and later in life to develop late onset diabetes.

The physiological changes are more gross in that we are dealing not with the subtleties of cellular and subcellular mechanisms. The physiological changes which take place and which ultimately lead to the detriment of the body are initially made in the hope of making the best of rather a bad metabolic job on the part of subcellular mechanisms.

It is these latter insidious subcellular changes which are marked by syndromes, which are pointers already described by the founding fathers of Orthomolecular medicine, and which will ultimately prove to be the basis of the diagnostic skill of the Orthomolecular physician of the future. We shall then no longer see doctors dealing with crisis medicine — the early-warning signs of which have remained undetected for years — but we shall see them fulfilling the role which I believe it is our duty to fulfill (that is, of preventative medicine), preserving the health of our patients, and adding years to their life and life to their years.

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