Critical Review

Chromium in Human Nutrition: A Review

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ABSTRACT This review summarizes the results of 15 controlled studies supplementing defined Cr(III) compounds to subjects with impaired glucose tolerance. Three of these (3–4 μmol Cr/d for >2 mo) produced no beneficial effects: serum glucose, insulin and lipid concentrations remained unchanged. The remaining 12 interventions improved the efficiency of insulin or the blood lipid profile of subjects (ranging from malnourished children and healthy middle-aged individuals to insulin-requiring diabetics). In addition, three cases of impaired glucose tolerance after long-term total parenteral alimentation responding to Cr supplementation have been reported. Chromium potentiates the action of insulin in vitro and in vivo; maximal in vitro activity requires a special chemical form, termed Glucose Tolerance Factor and tentatively identified as a Cr-nicotinic acid complex. Its complete structural identification is a major challenge to chromium research. The development and validation of a procedure to diagnose chromium status is the second challenge. Such a test would allow the assessment of incidence and severity of deficiency in the population and the selection of chromium-responsive individuals. The third challenge is the definition of chromium's mode of action on parameters of lipid metabolism that have been reported from some studies but not others. Future research along these lines might establish whether chromium deficiency is a factor in the much discussed "Syndrome X" of insulin resistance. J. Nutr. 123: 626–633, 1993.

INDEXING KEY WORDS:

- *chromium* • *humans*
- *glucose tolerance* • *insulin resistance*

A requirement for chromium to maintain normal glucose tolerance in rats was first demonstrated in 1959 (Schwarz and Mertz 1959). That demonstration was followed by reports of improved glucose tolerance by chromium supplementation in human subjects (Glinsmann and Mertz 1966) and by the demonstration of chromium deficiency and its reversal in patients receiving total parenteral nutrition (Brown et al. 1986, Freund et al. 1979, Jeejeebhoy et al. 1977). The results of two double-blind, crossover studies of chromium supplementation demonstrated beneficial effects in human subjects with mildly impaired glucose tolerance (Anderson et al. 1983 and 1991). The results of these and other studies form the basis for the following hypotheses: *1*) Marginal states of chromium nutriture contribute to the progressive impairment of glucose tolerance with age, typical in several industrial societies. *2*) Marginal chromium deficiency may increase the risk for diabetes (Mertz 1969) and, possibly, coronary heart disease (Schroeder 1968). The Food and Nutrition Board of the U.S. National Research Council suggested a range of safe and adequate intakes for chromium of 1 to 4 μmol/d (Food and Nutrition Board 1989). Studies of a World Health Organization Expert Committee (WHO Expert Committee 1973) and of the International Programme on Chemical Safety (IPCS International Programme on Chemical Safety 1988) described trivalent chromium as an essential nutrient with typical intakes of from 1 to 4 μmol/d.

Yet, the practical aspects of chromium nutrition are remarkably different from these considerations. At present, chromium is not accepted by the medical profession as the only therapeutic modality for diabetics, which is consistent with the conclusions of the first chromium supplementation study in humans (Glinsmann and Mertz 1966). More surprising is the lack of interest in the preventive aspects of chromium in human health, namely the promise to prevent or delay the deterioration of glucose tolerance with increasing age in a large number of people (Anonymous 1988). Possibly as a result of this attitude, the general public receives advice, promises and a multitude of chromium preparations from the "health food" industry, often accompanied by claims of "glucose tolerance factor activity." Relatively little has been published recently related to the physiological action of trivalent chromium, and the scientific literature is dominated by toxicological studies of hexavalent chromium, which, in a few compounds and applied via a special route, is carcinogenic in animals. I will attempt in the following review to evaluate the developments in chromium nutrition during the past 34 years and to summarize and assess the present state of knowledge.

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TABLE 1

Controlled chromium supplementation studies with identifiable chromium compounds

Authors	μmol Cr/d	Subjects	*n*	Results
Glinsmann and Mertz (1966)	3–20	Adult diabetics (USA)	6	Improvement of glucose tolerance test (GTT) in 3 of 6.
Hopkins et al. (1968)	5	Malnourished children (Jordan, Nigeria)	12	GTT improved; no effect in 5 controls.
Gürson and Saner (1971)	1	Malnourished children (Turkey)	14	Improvement of GTT in 9 of 14. No effect in 5 controls.
Mossop (1983)	40	Diabetics (South Africa)	13	GTT improved, HDL increased. No effect in 13 controls.
Martinez et al. (1985)	4	Elderly women not on medication, impaired GTT (Canada)	8	Significant improvement of GTT at reduced insulin response. No significant effect in 3 controls.
Anderson et al. (1983)	4	Middle-aged subjects with mild glucose intolerance (USA)	20	Significant improvement vs. placebo period.
Anderson et al. (1991)	4	Mildly glucose intolerant men and women on low Cr diet (USA)	8	Significant improvement of GTT vs. placebo period.
Riales and Albrink (1981)	2	Middle-aged men (USA)	12	Improved GTT at reduced insulin at 6 wk but not at 12 wk. Increase of HDL. No significant effect in 11 controls.
Wang et al. (1989)	1	Middle-aged men (USA)	10	Significant decrease of total and LDL cholesterol in Cr group. No change in 10 placebo controls. No effect on GTT. Some reduction of insulin response at 1 h only.
Uusitupa et al. (1983)	4	Noninsulin-dependent diabetics (Finland)	10	Reduction of insulin response at 1 h only. No effect on GTT.
Press et al. (1990)	4	Mildly hypercholesteremic subjects (USA)	28	Reduction of total and LDL cholesterol and apolipoprotein B. Increase of apolipoprotein A. GTT not measured.
Abraham et al. (1992)	5	Mildly hypercholesteremic subjects	76	Increase of HDL, reduction of triglycerides. No change in glucose, total cholesterol.

GLUCOSE METABOLISM IN HUMANS

Several human studies have been reported using a variety of chromium compounds, naturally occurring, semisynthetic or synthetic, with structures ranging from unknown to well defined. To evaluate and compare the results I will discuss only those that dealt with chemically defined compounds and used proper controls.[1] Three of the 15 studies meeting these criteria reported negative findings: daily chromium supplements of up to 4 μmol did not improve impaired glucose tolerance, reduce insulin levels to suggest an enhanced effectiveness of the hormone, or affect blood lipid concentrations. The studies supplied either 3 or 4 μmol of chromium in form of chromium chloride for periods between 2.5 and 4 mo. The subjects were four middle-aged males with normal glucose tolerance and 10 with mild diabetes (Sherman et al. 1968), 23 well-nourished elderly men and women (Offenbacher et al. 1985) and 43 outpatient diabetics of whom half were prone to ketosis (Rabinowitz et al. 1983).

The remaining 12 studies showed positive effects of chromium supplementation in malnourished children from Jordan, Nigeria and Turkey, in healthy middle-aged volunteers of both sexes from North America and in insulin-requiring diabetics from South Africa (Abraham et al. 1992, Anderson et al. 1983 and 1991, Glinsmann and Mertz 1966, Gürson and Saner 1971, Hopkins et al. 1968, Martinez et al. 1985, Mossop 1983, Press et al. 1990, Riales and Albrink 1981, Uusitupa et al. 1983, Wang et al. 1989). Studies that did not use control subjects, even those reporting positive outcomes, are not discussed here, which leaves the data reported in **Table 1** as the basis for the following evaluation:

1. Response to chromium supplementation: An impaired glucose tolerance can be improved or normalized by chromium supplementation or can be

[1]The data of Glinsmann and Mertz (1966) are included because of close control of food composition, food intake and physical activity of the subjects during the study in a metabolic ward.

maintained in spite of a reduced insulin output, but a normal glucose tolerance is not further improved. If chromium is accepted as an essential nutrient, not as a drug, its apparent effect, like that of any other essential nutrient, depends on the nutritional status of the test subjects. It improves an impaired function or restores it to normal, if that impairment developed because of chromium deficiency. Although impaired glucose tolerance is a consequence of chromium deficiency, it has many other causes and is therefore inadequate as the sole diagnostic criterion for chromium status. At present there are no specific tests available to diagnose chromium status, prior to a supplementation trial. For this reason the response to chromium supplementation cannot be predicted under ordinary circumstances, which is consistent with the wide variation in the results described above. Recognizing this handicap and attempting to lessen its impact, Anderson et al. (1991) fed 17 middle-aged human volunteers a low chromium diet (<0.4 μmol/d) for 14 wk. After 4 wk of adaptation, chromium (4μmol) or placebo was given for 5 wk and the treatment crossed over for an additional 5 wk. There was no change in the nine control subjects who entered the study with a normal glucose tolerance test, but the glucose tolerance test of the eight subjects with impaired glucose tolerance deteriorated further during the placebo period and improved again significantly during chromium supplementation. Insulin and glucagon concentrations rose during the placebo period and fell again during the chromium period. This is the first study of experimentally induced, marginal chromium deficiency; its results fully support the postulate of chromium as essential for optimal insulin activity.

2. Dose response curve: The quantity of chromium in the form of identifiable chemical compounds used in the various human studies (Table 1) ranged from 1 to 40 μmol/d. No exact dose-response studies to chromium have been performed in human subjects, and no efforts have been made to determine the lowest effective dose. In the studies discussed here, supplements of 3 μmol or more have been found effective in some studies; thus, it is unlikely that insufficient dosage could account for negative outcomes. Higher amounts (12–40 μmol/d) may be needed for diabetics.

3. Other limiting factors: There is evidence from in vitro and animal studies that chromium must be complexed with certain ligands to be fully active. Nicotinic acid and glutathione have been demonstrated to be components of a chromium complex exhibiting superior in vitro activity (Toepfer et al. 1977). A recent human study raised the possibility that nicotinic acid may become limiting, in addition to chromium under certain conditions. Human volunteers improved their glucose tolerance when 4 μmol of chromium and 0.8 mmol of nicotinic acid were supplemented together, but not with either nutrient alone (Urberg and Zemel 1987). Although this observation deserves careful follow-up, it probably does not provide the full explanation for the negative outcome of some chromium supplementation trials. Multiple deficiencies are more likely to occur in malnourished individuals than in those consuming typical Western diets; however, malnourished children responded promptly to chromium supplementation in several studies (Gürson and Saner 1971, Hopkins et al. 1968).

4. Geographic distribution: It is surprising to note that the response to chromium supplementation is stronger in developing countries with nutritional problems than it is in North America. If one study in malnourished children in Egypt is excluded from the evaluation because of generally high chromium intake and because chromium was supplemented only for 3 d (Carter et al. 1968), all trials in these areas reported impressive improvements of glucose tolerance with chromium supplementation. This response may possibly be related to a more severe chromium deficiency in the populations of those areas, in contrast to a more marginal situation in the developed countries.

5. The magnitude of the chromium effect: The degree of functional improvement should depend on dosage and timing of the supplementation, but dose-response relationships have not yet been studied systematically. The degree of improvement in response to chromium also depends on the degree of impairment. Restoration of the slightly impaired glucose tolerance of middle-aged North Americans to normal is associated with a statistically significant but clinically not very impressive improvement. With greater severity of chromium deficiency in malnourished children or in patients on total parenteral nutrition, the degree of impairment and of subsequent improvement becomes clinically important.

TOTAL PARENTERAL NUTRITION

Three cases of chromium-responsive glucose intolerance during total parenteral alimentation have been described (Brown et al. 1986, Freund et al. 1979, Jeejeebhoy et al. 1977). They had in common a long induction period of 7 mo or more, impairment of glucose tolerance with pronounced insulin resistance and unexplained weight loss. One case was complicated by peripheral neuropathy (Jeejeebhoy et al. 1977), the second case showed indications of encephalopathy (Freund et al. 1979), but the third had no evidence of any neurological malfunction (Brown et al. 1986). Intravenous administration of chromium (as chromium chloride) up to 5 μmol/d almost immediately restored normal insulin sensitivity and glucose tolerance and improved the other signs and symptoms that had developed during the low chromium period.

In evaluating the three reported cases of chromium-responsive impairment of glucose

tolerance during total parenteral nutrition, it is evident that the clinical signs and their prompt response to chromium supplementation correspond to the criteria of chromium deficiency as postulated from animal experiments. A critical review can find fault in the analytical aspects: chromium concentrations in all three patients were stated to be "at or below the lower limits of normal values according to the method employed," but the numerical values did not agree with each other, and what was reported as a deficient concentration in one case could be considered as superadequate in another. This does not invalidate the clinical results; it is due to the state of chromium analysis, which until recently was inadequate and which will be discussed later in some detail.

Another problem in interpreting the results lies in the small number of reported positive responses as compared with the multitude of total parenteral nutrition cases in which no impairment of glucose tolerance was observed. This can be explained by the great variability in the chromium concentrations of the solutions used during the earlier times of long-term total parenteral nutrition. Trace amounts of chromium were then, and in many instances are still, present as contamination, often adequate to cover the needs. More recently, following the recommendations of the American Medical Association, sufficient amounts of chromium are being added to the intravenous solutions, at least in the United States (AMA Department of Food and Nutrition 1979, Section on Clinical Nutrition 1984). Whenever such solutions are used the occurrence of chromium-responsive impairment of glucose tolerance would seem unlikely.

Finally, the reported involvement of the peripheral or central nervous system during total parenteral nutrition requires some discussion. The existence of peripheral neuropathy was well documented by objective measurements and, as a consequence of long-standing diabetes, is entirely plausible, even though it has not been reported in animal experiments. As the third published report (Brown et al. 1986) demonstrates, neuropathy is not present in all cases; therefore, it should not be considered an obligatory sign of chromium deficiency.

THE STATE OF CHROMIUM ANALYSIS

The essential function of chromium for maintenance of normal glucose tolerance in rats was postulated in 1959, at a time when atomic absorption spectroscopy was introduced into the laboratory and began replacing the older colorimetric analytical methods. Reported "normal" values in blood plasma or serum began to decline from several hundreds to ~0.75 μmol/L. The introduction of the graphite furnace reduced the values further, but only after the use of the more efficient background correction did the reported values stabilize in the range of 1 to 10 nmol/L; these values were confirmed by independent methods, such as isotope dilution mass spectrometry (Veillon 1989). Such low concentrations require the strictest control of contamination by performing sample preparation and analysis in ultra-clean rooms and by constant quality control with the use of standard reference materials that are now available. With these precautions, chromium analysis in biological materials is now routine in a few specialized laboratories. Analytical values reported before 1980 should not be accepted, and those reported more recently should be accepted only if accompanied by statements of proper quality control through certified reference materials.

As is also true for several other essential trace elements, there is no reliable analytical method to determine the nutritional chromium status of a person. Circulating chromium is not in equilibrium with the biologically important stores. Chromium concentration in hair may indicate status of large groups but not of individuals (Saner 1980). Chromium excretion in urine reflects the recent intake but has not been found useful in predicting the chromium status. The physiological interpretation of acute changes of plasma chromium following a glucose or insulin load is still controversial and requires future research.

EFFECT OF CHROMIUM ON LIPID METABOLISM

More than twenty years ago, Schroeder (1968) summarized his hypothesis that chromium deficiency represented a significant risk factor for cardiovascular disease. This hypothesis originated from his and Tipton's observations (Schroeder et al. 1962) of a reduced chromium concentration in the aortas of subjects dying from heart disease, as compared with those killed by accidents. Also, the authors observed marked differences in the geographic distribution of tissue chromium concentrations, suggesting a negative correlation between chromium status and cardiovascular disease risk. That hypothesis was consistent with observations on risk factors for cardiovascular disease in rats kept in a strictly controlled, low chromium environment, consisting of increased occurrence of aortic plaques and elevated blood lipids. These results have been confirmed by some but not all studies; of particular interest is the observation of a reversal of established atherosclerosis in the aorta of cholesterol-fed rabbits by daily chromium injections (Abraham et al. 1991). Most of the controlled studies used brewer's yeast as the source of the chromium-containing glucose tolerance factor. Of the eight controlled studies with identified chromium compounds,

four found no effect of 4 μmol of chromium per day on blood lipids (Anderson et al. 1983 and 1991, Offenbacher et al. 1985, Rabinowitz et al. 1983). Four equally controlled interventions with 4 μmol of chromium per day gave positive results. Twelve subjects with elevated total cholesterol levels reacted to chromium with a significant increase of their HDL cholesterol. The total cholesterol concentrations remained stable in the chromium-supplemented group and increased slightly in the placebo group (Riales and Albrink 1981). Very similar results were obtained in the most recent study (Abraham et al. 1992), in which 76 patients with elevated serum cholesterol were supplemented with 5 μmol/d of chromium (as chloride, n = 40) or placebo (n = 36) for an average of 11 mo. Although neither serum glucose nor total cholesterol improved, there was a significant increase in the HDL (from 0.94 to 1.14 mmol/L, $P < 0.005$) in those receiving the supplement. In the third study, chromium supplementation resulted in a 6% reduction of total cholesterol, compared with a 6% increase in the controls (Wang et al. 1989).

Four micromoles of chromium as picolinate given to subjects with elevated serum cholesterol for 6 wk resulted in a significant 6.9% reduction of total cholesterol, a 10.9% reduction of LDL cholesterol and a 5.7% increase of HDL cholesterol (Press et al. 1990).

The relation of serum chromium concentrations to coronary artery disease was investigated in two independent studies (Newman et al. 1978, Simonoff et al. 1984) using a total of 122 patients, of whom 82 were diagnosed by cine-arteriography as having coronary artery disease. Although the reported chromium levels were too high by present standards, they differed significantly between subjects with coronary involvement and those diagnosed as normal. The mean chromium concentration in patients was lower by 41% (Newman et al. 1978) and 12% (Simonoff et al. 1984), respectively, compared with the corresponding healthy controls.

The contradictory results of these trials are difficult to reconcile. Disturbances of lipid metabolism including hypercholesterolemia were not originally included among the criteria for chromium deficiency and were not part of the clinical picture observed in the three defined cases of chromium deficiency in total parenteral nutrition. In view of the many known nutritional influences on lipid metabolism it is probably reasonable to assume that only certain cases are related to a low chromium status through impairment of glucose tolerance, and that only those cases would be expected to improve with chromium supplementation. Controlled human studies are needed to establish an effect of chromium on lipid metabolism and to find a basis for a theory concerning the mode of action. Because of the present lack of a reliable diagnostic test for chromium status the responders cannot be predicted.

CHROMIUM METABOLISM

The dynamic behavior of chromium in blood and urine following a glucose challenge holds promise for future research. The observation of acute increments of plasma chromium during a glucose tolerance test in normal subjects, the lack of such an increment in some diabetics and its reappearance following chromium supplementation in these same diabetics suggested a physiological function of the chromium increment (Glinsmann et al. 1966). Other investigators observed the opposite, an acute decline of chromium concentrations, following a glucose challenge (Davidson and Burt 1973). Those early results were obtained with inadequate analytical methods yielding values that were too high but have been repeated more recently with more accurate methods. An explanation for the apparently contradictory results (increase in some studies vs. decrease of chromium concentrations in other studies) was offered by Liu and Abernathy (1982) in a study that measured the chromium response by neutron activation analysis, together with glucose tolerance, serum insulin response, body weight and triceps skinfold thickness. When the 20 subjects were divided into two groups according to their insulin response to the glucose challenge, only those subjects with a low, normal insulin response (total area of insulin under the curve, 2.5 nmol/L) showed a mean increase in chromium concentration of 98% in response to the glucose challenge. In contrast, the high insulin group (total area of insulin under the curve, 5.2 nmol/L), which also had a significantly higher mean body weight, showed a decline in serum chromium concentration of 24% in response to the glucose challenge. These two opposite patterns are compatible with the hypothesis that any increase of circulating insulin results in the binding of chromium to peripheral, insulin-sensitive tissue, possibly to insulin receptors. Thus, during a glucose tolerance test, chromium either could be released immediately from adequate stores and appear in the circulation, or it could be taken from the circulation if the stores were inadequate, resulting in a temporary decline. In any case, the results clearly indicate a greater effectiveness of insulin in the presence of the chromium increment than in its absence. Because the authors had previously shown that a negative chromium response could be made positive by supplementation with high chromium yeast, they suggested the use of the relative chromium response as an indicator of chromium status. Although this theory awaits confirmation by independent studies, all available data indicate that glucose metabolism, most probably via changes in circulating insulin, influences circulating chromium concentrations. Identification of the chemical nature of the plasma chromium increment is an important goal of chromium research.

THE GLUCOSE TOLERANCE FACTOR

Soon after the description of an in vivo effect of chromium in rats, in vitro studies with rat epididymal fat tissue demonstrated a significant effect of chromium on in vitro glucose utilization (Mertz et al. 1961) as well as cell transport of D-galactose (Mertz and Roginski 1963). The effect was that of a potentiation of exogenous insulin as demonstrated by a significantly greater slope of the insulin dose-response curve in the presence of chromium. The search for greater bioactivity led to the in vitro testing of many well-defined synthetic complexes and of less well-defined chromium compounds. Purification of the insulin-potentiating activity from brewer's yeast produced preparations of high biological activity and led to the identification of compounds in which two molecules of nicotinic acid and amino acids, probably the constituents of glutathione, are coordinated to chromium. Mixtures of synthetic compounds of that composition proved to be nearly identical in their physical chemical characteristics to active, purified yeast preparations (Toepfer et al. 1977). They were highly active in the in vitro system, and they acutely improved glucose and blood lipid concentrations in genetically obese diabetic mice in which simple chromium compounds such as chromium chloride were ineffective (Tuman et al. 1978). Attempts to further purify these mixtures of closely related compounds to isolate, identify and crystallize individual species have been unsuccessful. The uncertainty relating to the exact structure of the glucose tolerance factor may be responsible for contradictory publications concerning its nature. Although two groups agree with the results described above (Mirsky et al. 1980, Yamamoto et al. 1989), others no longer consider glucose tolerance factor from brewer's yeast a chromium complex (Haylock et al. 1983), and a patent application has been filed in the United Kingdom describing glucose tolerance factor as a cobalt, rather than chromium, complex with niacin and glutathione (U.K. Patent Application GB 2 026 498 A 1978).

Substantial progress in our understanding of active chromium species was made by two research groups in Japan. Instead of using biological activity in vitro as the main criterion for purification procedures, they followed the pathway of administered chromium under various conditions and came to the following conclusions: Chromium, injected either intraperitoneally or intravenously, is incorporated into two chemical species for which physiological functions have been postulated, one of high-, the other of low-molecular-weight. The former is a 70-kDa protein, containing 5–6 atoms of chromium per molecule, corresponding to ~80 mmol/kg. This protein is induced in regenerating liver by the administration of chromium to partially hepatectomized rats. Chromium in this form can bind to nucleolar chromatin, resulting in significant stimulation of RNA synthesis (Okada et al. 1989). These observations suggest a regulatory role of the protein-bound chromium in nucleic acid synthesis, in contrast to the uncontrolled reaction of hexavalent chromium with genetic material. The demonstration of a chromium protein confirms the original observation by Wacker and Vallee (1959) of very high chromium concentrations in beef liver fractions consisting of 70% RNA and 30% protein.

A low-molecular-weight chromium-binding ligand was isolated from human urine, mouse liver and bovine colostrum (Yamamoto et al. 1989). Its function was originally thought to be detoxification, because the compound is induced by the injection of hexavalent chromium. It has a molecular weight of ~1500; its composition was stated as chromium, aspartic acid, glutamic acid, glycine and cysteine, and, although no nicotinic acid was detected, some substance absorbing at 260 nm was present. The compound exhibits some biological activity on glucose oxidation by isolated fat cells, very similar to that of the glucose tolerance factor preparations described by Toepfer et al. (1977). Thus, the compound seems to serve a physiological function, in addition to detoxification of hexavalent chromium. These biological effects are dependent on the presence of chromium in the molecule.

CONCLUSIONS

The results of the human studies reviewed here as well as data from in vitro and animal experiments lead to three conclusions: *1*) Chromium deficiency results in insulin resistance. *2*) Insulin resistance caused by chromium deficiency can be ameliorated by chromium supplementation. *3*) Chromium deficiency does occur in populations in the United States and elsewhere; it may be an important cause of insulin resistance in those populations.

Although insulin resistance, for example in middle-aged persons with impaired glucose tolerance, is not considered an indication for immediate medical treatment, it has raised much concern as a very significant risk factor for coronary heart disease. This was stated by G. M. Reaven as follows: "It now appears that resistance to insulin-stimulated glucose uptake and compensatory hyperinsulinemia are associated not only with states of IGT [impaired glucose tolerance], but are also seen in individuals with high blood pressure, hypertriglyceridemia and low plasma concentrations of high density lipoprotein cholesterol. All of these events have been identified as increasing the risk of coronary heart disease (CHD), and there is increasing evidence that they tend to cluster in the same individual. As a consequence, it has been suggested that this constellation of abnormalities constitutes a syndrome (X) that plays an

important role in the etiology of CHD. Indeed, in some populations it can be argued that Syndrome X is involved in the etiology of CHD to a greater degree than is an increase in plasma low-density lipoprotein (LDL) cholesterol concentration." (Reaven 1992). What is it then, that makes the area of chromium nutrition uninteresting to all but a few investigators, in contrast to the substantial interest in chromium toxicology? Why do we neglect the well-founded promise of controlling the deterioration of glucose metabolism with age in our population, before a mild insulin resistance turns into diabetes with its inherent risk factors for cardiovascular disease (Reaven 1992)?

There are two answers. Scientists and physicians must diagnose a condition before intervening in a system or a patient, but there is no a priori reliable method to diagnose chromium deficiency in an individual. Analysis was in a state of flux until a few years ago; although it is now reliable for many measurements, no physiologically meaningful pool has yet been defined. Thus, a positive response to supplementation cannot be predicted.

The other answer relates to the signs of mild chromium deficiency encountered in the United States population. The impairment of glucose tolerance, by definition, is not diabetes; it is even considered by some as a normal, age-related process of no immediate clinical importance. Yet, as discussed above, mild chromium deficiency is a risk factor for a spectrum of disturbances that are almost identical to those of Syndrome X (Reaven 1992), except for hypertension, which has not yet been studied in human chromium deficiency. Both conditions are not easily diagnosed in young or middle-aged people, and both are believed to occur at a high enough incidence to represent a significant public health problem. A role of dietary components in Syndrome X is considered probable (Foster 1989). The data reviewed here strongly support the postulate that chromium deficiency plays a major role.

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