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A DEFICIENCY OF VITAMIN B_6 IS A PLAUSIBLE MOLECULAR BASIS OF THE RETINOPATHY OF PATIENTS WITH DIABETES MELLITUS

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Eighteen patients with diabetes mellitus, some of whom had variously retinopathy, pregnancy, and the carpal tunnel syndrome, and were variously treated with steroids and vitamin B_6, have been overviewed for periods of 8 months to 28 years. We have established an association of a deficiency of vitamin B_6 with diabetes by monitoring the specific activity of the erythrocyte glutamic oxaloacetic transaminase and again by the association with the carpal tunnel syndrome (C.T.S.). It has been known for a decade that C.T.S. is caused by a B_6 deficiency. The absence of retinopathy in vitamin B_6-treated diabetic patients over periods of 8 months - 28 years appears monumental. These observations are like discovery and constitute a basis for a new protocol to establish the apparent relationship of a deficiency of vitamin B_6 as a molecular cause of diabetic neuropathy. Blindness and vision are so important that the strength or weakness of the observations are not important; the conduct of a new protocol is important.

Many physicians have studied diabetes mellitus in relation to other diseases. Association of diabetes with retinopathy has long been known, and an overview of diabetic retinopathy includes pregnancy and therapy with steroids.

Phalen (1) reported that of 103 patients who had surgery for the carpal tunnel syndrome, 28 or 27% either had overt diabetes or a history of diabetes in their families. Consequently, there has been a frequent association of diabetes with the carpal tunnel syndrome.

Correlated biochemical research and clinical treatment of the carpal tunnel syndrome with vitamin B_6 at a daily dosage of 100-300 mg resulted in effective therapy, and obviated the common surgery on the hands to relieve the symptoms of this syndrome; Ellis, Folkers, et al. (2,3).

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This combined biochemical and clinical research on the carpal tunnel syndrome and treatment with vitamin B_6 included patients with associated diabetes, and also who had a deficiency of vitamin B_6 which ranged from unambiguous to severe. In general, the deficiency of vitamin B_6 was established by analysis of blood samples from patients having the carpal tunnel syndrome as based on the specific activity (S.A.; um pyruvate/hr./10^8 cells) of the erythrocyte glutamic oxaloacetic transaminase (EGOT); Folkers et al. (4,5). An S.A. of EGOT of 0.30 - 0.35 correlated with an unambiguous and common deficiency of vitamin B_6. A level of the S.A. which was below 0.3 would correlate with a severe deficiency of vitamin B_6. An oral dosage of vitamin B_6 at 50 - 200 mg, daily, over a necessary period of about three months, increased the level of the S.A. of EGOT to a maximum value of 0.69 ± 0.09.

Separate from the association of diabetes with the carpal tunnel syndrome, diabetes is frequently associated with pregnancy. Again, in overview, there can be an association of diabetes with all three physiological states, retinopathy, pregnancy, and the carpal tunnel syndrome. Over a period of nine years, Ellis (6) treated 225 pregnant women with a daily dosage of 50 - 200 mg of vitamin B_6, and the carpal tunnel syndrome of 25 of these 225 pregnancies (11%) was effectively improved by treatment with vitamin B_6 before parturition; Ellis and Folkers (7).

Our years of study of the association of diabetes, retinopathy, and the carpal tunnel syndrome, and treatment with vitamin B_6, have led to a biochemical and clinical interpretation, which approaches a conviction, and that is ---that the retinopathy which is associated with diabetes is a plausible consequence of a long-standing deficiency of vitamin B_6. This biochemical and clinical interpretation is like a discovery, and did not evolve from a protocol. However, this interpretation is now a basis for a new protocol which is designed to establish whether the retinopathy of diabetes is indeed a consequence of a vitamin B_6 deficiency, and whether treatment with vitamin B_6 of diabetic retinopathy can diminish or preferably eliminate the retinopathy. The importance of vision and blindness justifies the necessity of giving the benefit of the doubt to this biochemical and clinical interpretation regardless of the strength or weakness of the present evidence.

Previously, we reported our study of nine diabetic patients and the apparent association of retinopathy with a deficiency of vitamin B_6, and that treatment with vitamin B_6 appeared to prevent retinopathy or hold the neovascularization in abeyance; Ellis, Folkers, et al.

(8). Herein, we describe the results of our continuing study as based upon 18 patients with complicated diabetes mellitus.

RESULTS AND DISCUSSION

The eighteen patients whose diabetes was variously associated with retinopathy, pregnancy, and the carpal tunnel syndrome, as well as with various treatments with steroids, and in some cases, vitamin B_6, have been overviewed. Although a few of these patients were at times violently ill, with two requiring leg amputations, and with two requiring psychiatric care, and one expiring during an evaluation period of 18 months, the focus of this study of these 18 patients has been on their retinas and particularly on any changes in pathology without and with treatment with vitamin B_6 for long periods of time.

The existance of significant to severe deficiencies of vitamin B_6 in some of these diabetic patients was established both by the 10 - year knowledge of the biochemistry of the specific activities (S.A.) of the erythrocyte glutamic oxaloacetic transaminase (EGOT), which verifies the existance of a B_6 deficiency, and the very overt clinical symptoms of the carpal tunnel syndrome. This syndrome was established to respond effectively to oral therapy with vitamin B_6. Six of 17 diabetic patients had been treated with vitamin B_6, at 50 - 200 mg daily, for periods of eight months - 28 years, and these six B_6-treated patients revealed not one sign of diabetic retinopathy. Three of the additional patients who had been treated with B_6 revealed only minimal diabetic retinopathy. Two additional patients making a total of 11 of 17 patients treated with vitamin B_6 either had no retinopathy or revealed dimunition or stabilization of retinopathy. Two other patients had developed proliferative retinopathy during treatment with vitamin B_6 which required laser surgery. One additional patient revealed no neovascularization, but required laser surgery. Another patient, for a total of the 18, at age 73, was severely deficient in vitamin B_6, by the S.A. of EGOT, and after 14 years of diabetes, and being insulin-dependent for 13 years, revealed diabetic retinopathy.

Altogether, 6 of these 18 patients revealed a severe deficiency of vitamin B_6, by the S.A. of EGOT, either before treatment with B_6 or because of non-compliance during treatment.

The improvement or dimunition of diabetic retinopathy was most clearly evident when the treatment with vitamin B_6 was during the pre-proliferating stage of the retinopathy. It appeared that in the

presence of pregnancy and a crisis of diabetes, the deficiency of vitamin B_6 was a precursor of the diabetic retinopathy.

Pyridoxine (commonly known as vitamin B_6), pyradoxamine and pyridoxal are the three compounds of the so-called vitamin B_6 group which are widely distributed in nature. The phosphate of pyridoxal is the particularly important coenzyme (pyridoxal-5-phosphate) which is so indispensibly functional in amino acid metabolism.

An analogy between a microbial and mammalian deficiency of pyridoxine and/or the coenzyme over a prolonged time may be severe limitation of microbial growth and a mammalian nutritional disease. In the research on codecarboxylase (pyridoxal-5-phosphate), Bellamy et al. (9) recognized that microbial growth without vitamin B_6 occurred when there was microbial biosynthesis of codecarboxylase. Lwoff et al. (10) initially recognized the essentiality of "factor V" for microbial growth, which was elucidated as coenzymes I and II and which would activate microbial activity within 60 seconds. A very prolonged mammalian (human) deficiency of the coenzyme of vitamin B_6 by analogy to microbial growth may be expected to be a cause of disease. In this research on diabetes, retinopathy may result from the deficiency of vitamin B_6.

Experience over years on treatment revealed that a dosage of 50 mg daily of vitamin B_6 was appropriate for prevention of diabetic retinopathy in children, and that a corresponding dosage of 100-200 mg daily was appropriate for adults; both being indefinitely treated and with compliance.

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