

Reply to a Commentary by Elstein et al. on the paper by Cohen IJ et al. *BCMD* 24:296- 302, 1998

Elstein et al. (1) suggest that it is unclear how the 10 patients were chosen from a group of 18 published previously. It is evident from the patients and methods section of the original article (2) that 5 were not included because they were treated with imiglucerase, and one other child received 120 Units/kg/month. From the article itself (3), it is clear that only 10 of these 12 filled the criteria for severe juvenile onset type 1 Gaucher disease.

We agree that the prevalence and intensity of bone crises tends to decrease with puberty and early adulthood. It would have been relevant to comment on this if there had been a difference between the different age groups or the results had been “too good to be true”. However, the opposite was the case. No claim was made for the preference of one regime over another in our article, since only the results of one regime were presented.

We have no complaints about the criteria of the original Joint Gaucher Committee in Israel, who initially started treatment of the most seriously affected patients. It was also appropriate to broaden the criteria when it was found that the Ministry of Health could cope with the cost. Clearly these patients received inadequate therapy since they continued to suffer from bone crises. This has nothing to do with the question of what is adequate therapy.

We were surprised that Elstein et al. found justification from the article by Mistry et al. (4) for using “60 units /kg/month as a starting regimen in small children, primarily to ensure linear growth”, since the dose recommended in this article is 60 units/kg every other week. No claim is made in the article that, for linear growth, a higher dose is better than a lower dose.

We specifically coined the category of “severe juvenile-onset type 1 Gaucher disease”

since they represent a distinct group of patients who require a special approach. The presentation of a group of less severely affected children are presented who, it is claimed by Elstein et al., are so similar to those in our article that they controvert the message that a distinct group of patients exist who should be defined and treated differently. There seems to be some confusion regarding the exact meaning of “symptoms”. These are *subjective* disturbances caused by disease. This is quite distinct from “physical signs”, which are *objective* marks of disease, appreciated by the trained observer using his senses (5). Thus symptomatic disease is reported in the patients described in the commentary. In spite of the claim that the children had systemic disease (all that is indicated is that they had a mean Hb of 9 gm% and a mean spleen excess=27 fold). This inexact use of language leads to confusion. Some of these patients may have been among those reported in another report (6) from this group as having “symptoms at presentation” such as - sister’s disease. The patients mentioned in the commentary presented under the age of six but would not have been included in the present study since they did not have inclusion criteria for severe juvenile onset type 1 Gaucher disease, especially with respect to the occurrence of bone crises and a young age at splenectomy. It would seem that they also were not eligible for therapy by the Ministry of Health criteria and therefore were treated “primarily from private funds or compassionate care by the smaller health care schemes”. It should be noted that the NIH consensus conference did not advocate treatment of asymptomatic patients (7).

Although the patients treated by Elstein et al. presented before the age of 6 years they began therapy before the age of 10 years. In spite of this delay they had no evidence of skeletal complications. This is clearly different from the natural history of the children with severe juvenile onset Gaucher type 1 disease who developed bone crises and even fractures before the age of 10 years. On the other hand it is difficult to assess the data. The claim that there was no “incidence

of bone pain/crises, pathological fractures or avascular necrosis in nearly 8 years of follow up” is not substantiated by a previous report (8). This would suggest that in fact only 1 patient had been followed for 8 years and all others for less. Although it is claimed that none of the patients were splenectomized the article cited mentions only patients who underwent partial splenectomy. No nonsplenectomized patients were mentioned in the report (9).

Elstein et al. “prefer non-steroidal anti-inflammatory drugs for pain management and if necessary, narcotics that can be patient-controlled even by adolescents; failure of narcotic therapy typically implies insufficient and inappropriate administration”. Unfortunately this is not true since patients may be hospitalized for weeks of intravenous narcotics during which time they presumably continue to be symptomatic. As pediatric hematologists/oncologists we have no fear of using adequate doses of narcotics but the problem is that the pain “often cannot be relieved even by narcotics (10).” “The severity is attested to by the recognized difficulty in controlling the pain, even with an intensive narcotic program” (11). The use of oral short term ambulatory high dose prednisolone has been revolutionary; the pain being relieved in hours. One mother, whose child suffered a second bone crisis could not understand why we phoned to ask how her son was feeling, the following day. She had seen the pain dissipate within hours of the previous attack and was sure this is what was to be expected. She was surprised that we were worried. Elstein et al. express concern about side effects but pediatric hematologists are used to high-dose glucocorticoid treatment for conditions such as idiopathic thrombocytopenic purpura, aplastic anemia, myelofibrosis, relapsed leukemia, in the treatment of acute nonlymphocytic leukemia, acute lymphocytic leukemia (12), and Diamond-Blackfan anemia (13). The complication of cardiovascular collapse reported after rapid intravenous therapy is avoided by using oral prednisolone.

We have continued to use this treatment since

1994 and have not seen any complications in patients on enzyme replacement therapy. Since 1991 we have not seen a fractures in any patient on enzyme replacement therapy including those who have received high dose prednisolone on more than one occasion. We unequivocally recommend this treatment modality in children and young adults on enzyme replacement therapy.

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