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Preliminary proposal for research on the
BAIB metabolic polymorphism
in human subjects.

BAIB (b-amino-isobutyric acid) is an intermediate product of thymine metabolism that has appeared in human urine in a variety of perplexing circumstances U1e. It now appears that it may be excreted in large amounts either a) in subjects who are homozygous for the enzyme BAIB-pyruvate transaminase U2e; or b) in subjects who are experiencing abnormal levels of thymine catabolism, probably mainly from the thymine- ribonucleotide of transfer-RNA rather than from DNA U3e.

Thymine overload has been associated, in turn with a variety of conditions, prominently but not exclusively neoplastic; and occasionally, perhaps, with excessive dietary intake. However, it has been difficult to unravel the diagnostic signficance of BAIB-uria , or to complete the genetic study of the metabolic polymorphism for lack of a non-invasive test for the transaminase. There is good reason, however, to believe that 40-50% of orientals, but only about 2% of caucasians, are recessive homo- zygotes; and it is difficult to understand such variations in gene frequency except as a polymorphism, namely that some disease process is mitigated in the BAIB-heterozygotes (by analogy with the Hb-S/Hb-A advantage of the sickle-cell trait in resisting malarial infection).

Conversely, the significance of excessive BAIB output as a measure of tissue pathology is difficult to assess without a reliable method of classifying the transaminase +/- genotypes. At present, the liver is the only tissue known to manifest the enzyme; and liver-biopsy cannot be advocated for routine research screening.

Having already learned a good deal about the analysis of BAIB by techniques of combined gas chromatography/mass spectrometry (GC/MS), we propose to develop non-invasive methods of studying BAIB metabolism, and of classifying these genotypes. The principal methods will a) use synthetic stable-heavy-ispotope labelled BAIB and its precursor, thymine, to establish body pool sizes by isotope dilution, and the rate of metabolism in persons whose excretion patterns of BAIB have been established; and b) parallel development of a method of enzyme assay to identify the activity of the D-B-aminoisobutyrate:pyruvate enzyme (responsible for BAIB degradation) in tissue or blood, if present, to correlate the results of (a) with enzyme activity. Both (a) and (b) will use the sensitivity and specificity of GC/MS in conjunction with selected ion monitoring to quantitate levels of BAIB and its metabolites.

We then propose to reexamine the correlation of BAIB-uria, BAIB-emia, and protein-bound plasma BAIB with disease processes in children's urine, and in samples of amniotic fluid obtained in pregnancies already identified as being of high risk of congenital disease. We will investigate levels of maternal urinary BAIB and levels of BAIB in amniotic fluid over the course of such pregnancies as a potential indicator of fetal well-being. Although elevated levels of BAIB have been reported in newborns U4,5e, measurement of levels during pregnancy and the relationship of BAIB to disease states have not been investigated.

The very least that can be expected, with confidence, from these studies, is the understanding of a widespread and puzzling polymorphism; and there is an excellent chance that this will also relate to the earlier detection and understanding of specific congenital diseases.

SUNEX. 2

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