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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 [1]. It now appears that it may be excreted in large amounts either a) in subjects who are homozygous for the enzyme BAIB-pyruvate transaminase [2]; 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 [3].

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.

Perhaps of most immediate relevance to prenatal health, we also plan to investigate levels of BAIB in maternal urine during normal and complicated pregnancies, on the supposition that it may be a revealing indicator of the course of fetal growth. However, any such analysis will have to be unravelled from the other issues mentioned above.

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.

1] H. E. Sutton, "Beta-aminoaciduria" in "The Metabolic Basis of Inherited Disease", J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson, Eds., McGraw-Hill Inc., New york, N.Y., 1st Edition, 1960, p. 792.
2] K. Taniguchi, T. Tsujio, and Y. Kakimoto, "Deficiency of D-B-Aminoisobutyrate:Pyruvate Aminotransferase in the Liver of Genetic High Excretors of D-B-aminoisobutyrate," Biochim. Biophys. Acta, 279, 475 (1972).
3] H. R. Nielsen, K. Nyholm, and K.-E. Sjoiln, "Relationship Between Urinary B-Aminoisobutyric Acid and Transfer RNA Turnover in Cancer Patients," Cancer Res., 34, 3428 (1974).