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 Ule. 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 significance 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-isotope 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.
5e H. K. Berry, "Individual Metabolic Patterns: II. Excretion of Beta-Aminoisobutyric Acid," Metabolism, 9, 373 (1960).