Any reduction in work should provide sufficient selective advantage to lead us to expect that a species whose habits meet the physical requirements will capitalize on passive ventilation. Furthermore, demonstration that active pumping can be adequate to meet an animal's respiratory needs does not constitute evidence that the animal cannot benefit from passive ventilation. All of the studies cited by Hoffman and Mangum were carried out under experimental conditions which completely precluded passive ventilation. Even Krüger (*1*) employed a bell jar over one end of the *Arenicola* burrow. We do not question any of these results but merely suggest that another phenomenon of potential significance may have inadvertently been overlooked.

Does *Arenicola* plug its burrow between bursts of pumping? Wells (*2*), commenting on his observation of a worm in a glass tube beneath still water, stated only: "In the relatively quiet intervals between outbursts, the worm was lying in the curved part of the U, with its head toward the float and its body rather short and thick." He further noted that "worms appear to be more active between the bursts when in sand than they are in glass tubes." For worms that make single-ended burrows, however, passive ventilation can be disadvantageous; viscous entrainment at the aperture will reduce the pressure in the burrow and may draw water from anoxic sediments into it. Thus plugging of burrows might be expected in some of the other species mentioned by Hoffman and Mangum.

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References and Notes

1. F. Krüger, *Helgoländer Wiss. Meeresunters.* **11**, 70 (1964).
2. G. P. Wells, *J. Mar. Biol. Ass. U.K.* **28**, 447 (1949).

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Lipid Biosynthesis and Increase in Isovaleric Acid of Plasma

Tanaka *et al.* (*1*) reported that the administration of hypoglycin A, a causative agent of Jamaican vomiting sickness, results in an increase in isovaleric acid in the plasma of rats. They suggested that the increased levels result from an overloading of the glycine conjugating system. In isovaleric acidemia, a disease with parallel symptoms, the increase in isovaleric acid is explained in terms of the inhibition of isovaleryl coenzyme A (CoA) dehydrogenase (*2*).

However, an additional pathway involving lipid biosynthesis may also be operative. Horning *et al.* (*3*) have shown that in a partially purified soluble enzyme system from rat adipose tissue isovaleryl CoA is readily condensed with malonyl CoA in the biosynthesis of long-chain iso acids. Under the experimental conditions, the isovaleryl CoA is incorporated at a rate almost comparable to that of acetyl CoA. A notable example of isovaleric acid "detoxification" is found in porpoise acoustic tissues where large amounts of lipids containing isovaleric acid and long-chain iso acids are deposited (*4*). Accordingly, enzymes capable of incorporating isovaleryl CoA into lipids are present in normal mammalian tissues. The fact that only small amounts of the iso acids are usually found simply reflects the low concentrations of isovaleryl CoA present (*3*). Therefore, we suggest that blocking of incorporation of the isovaleryl CoA in lipid biosynthesis may be an additional factor in the accumulation of isovaleric acid in the plasma of patients inflicted with the Jamaican vomiting sickness or isovaleric acidemia.

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References

1. K. Tanaka, K. J. Isselbacher, V. Shih, *Science* **175**, 69 (1972).
→ K. Tanaka, M. A. Budd, M. L. Efron, K. J. Isselbacher, *Proc. Nat. Acad. Sci. U.S.* **56**, 236 (1966).
3. M. G. Horning, D. B. Martin, A. Karmen, P. R. Vagelos, *J. Biol. Chem.* **236**, 699 (1961).
4. U. Varanasi and D. C. Malins, *Biochemistry* **9**, 3629, 4576 (1970); *Biochim. Biophys. Acta* **231**, 415 (1971).

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We have demonstrated that the accumulation of the isovaleryl moieties (isovalerate + isovalerylglycine) seen in both isovaleric acidemia (*1*, *2*) and hypoglycin-treated rats (*3*, *4*) is due to the depression of leucine oxidation at the stage of isovaleryl CoA dehydrogenase. Thus, isovaleryl CoA is not oxidized further (*1*, *3*); but is alternatively conjugated with glycine (*2*–*4*). Consequently, a large amount of isovalerylglycine is excreted in urine in both cases (*2*, *4*). When the amount of isovaleryl CoA exceeds the capacity of the glycine acylating system, the excess would be hydrolyzed, resulting in a release and accumulation of free isovaleric acid (*2*, *4*). The derangement of leucine metabolism in isovaleric acidemia is identical to that in hypoglycin-treated rats. The basic difference is that the former is due to the genetic deletion of isovaleryl CoA dehydrogenase, whereas the latter is induced by inhibition of the same enzyme.

Branched long-chain fatty acids are minor components in mammalian lipids (*5*). It has been known since 1823 that fats from some tissues of dolphins and porpoises are unique in containing a considerable proportion of isovaleric acid (*6*). Isovaleric acid has never been identified as a component of lipid from other mammals.

There is no reason therefore to speculate that blocking of incorporation of isovaleryl CoA into lipid biosynthesis is another contributing factor to the pathogenesis of the two diseases. As a rule, inborn errors of metabolism are usually the result of single enzyme deletions, and to postulate a deletion of two enzymes, without evidence, seems unnecessary.

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References and Notes

→ K. Tanaka, M. A. Budd, M. L. Efron, K. J. Isselbacher, *Proc. Nat. Acad. Sci. U.S.* **56**, 236 (1966).
2. K. Tanaka and K. J. Isselbacher, *J. Biol. Chem.* **242**, 2966 (1967).
→ K. Tanaka, E. M. Miller, K. J. Isselbacher, *Proc. Nat. Acad. Sci. U.S.* **68**, 20 (1971).
4. K. Tanaka, K. J. Isselbacher, V. Shih, *Science* **175**, 69 (1972).
5. A. T. James, J. E. Lovelock, J. P. W. Webb, *Biochem. J.* **73**, 106 (1959); W. Insul and E. H. Ahrens, *ibid.* **72**, 27 (1959); M. G. MacFarlane, G. M. Gray, L. W. Wheeldon, *ibid.* **74**, 43p (1960).
6. T. P. Hilditch and P. N. Williams, *The Chemical Constitution of Natural Fats* (Chapman and Hall, London, 1964), p. 33.

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