Burstyn, N. Durkin, N. L. Muiruri, *Lancet* **1971-II**, 352 (1971).
11. J. Meites, in *Methods in Investigative and Diagnostic Endocrinology*, S. A. Berson and R. S. Yalow, Eds. (Elsevier, Amsterdam, 1973), p. 609.
12. Y. Yamada, *Neuroendocrinology* **18**, 263 (1975).
13. J. A. Clemens, R. V. Gallo, D. I. Whitmoyer, C. H. Sawyer, *Brain Res.* **25**, 371 (1971).
14. I. S. Login and R. M. MacLeod, *ibid.* **132**, 477 (1977).
15. M. W. Brightman and T. S. Reese, *J. Cell Biol.* **40**, 648 (1969).
16. D. H. Ford, in *Reviews of Neuroscience*, S. Ehrenpreis and I. J. Kopin, Eds. (Raven, New York, 1976), p. 1.
17. This study was supported in part by grants from the Medical Research Council of Canada (MT-4182), the U.S. Public Health Service (1ROI, AM 19573-01), QRC Establishment grant 291-96, and MRC scholarship 24783.
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Nonhuman Models of Hereditary Porphyrias

While bovine protoporphyria may prove to be a more useful subject of clinical studies than any one of the numerous alternatives, it is not "the first known animal model for any of the hereditary human porphyrias other than so-called 'erythropoietic' porphyria" (*1*).

High levels of free porphyrins in living tissues occur in at least four phyla of multicellular animals in addition to the Chordata (*2*). A free porphyrin now known to be protoporphyrin IX was found in the annelid body wall as early as 1886, by the British zoologist MacMunn (*3*). In the 20th century, the wide zoological distribution of free porphyrins and the great structural diversity of naturally occurring compounds has been investigated extensively (*4*). Among the adults of a species the compounds are essentially ubiquitous, leaving little doubt of their hereditary basis. At least in the annelids and the asteroid echinoderms, exposure to daylight is often accompanied by the classical clinical symptoms of the human porphyrias, for example, cutaneous lesions, edema, and, eventually, death.

The interest in these facts is less the correction of a minor historical oversight and more the ecological and evolutionary aspects of the distribution of porphyrias. In phyla such as the echinoderms and nemertines, porphyrias (including protoporphyria) are found in species that do not have protoheme proteins in the blood or in nerve and muscle tissues (*2*). Thus there are nonhuman models that clearly cannot be associated with erythropoiesis, or related forms of protoheme synthesis. In the annelids, however, many of the porphyrias (also including protoporphyria) are associated with the biosynthesis of oxygen carriers in the blood, either of two high-molecular-weight extracellular heme proteins (*5*). Porphyrias have not been found in species with only intracellular blood oxygen carriers, suggesting an inherent advantage of the red cell environment in the control of the biosynthetic pathway (*6*).

Moreover, porphyrias are found only in annelid species or in parts of their bodies that do not normally encounter daylight; they do not seem to occur among the errant families or in respiratory and feeding organs, which are protruded from the darkness of the tube (*5*). Thus the inheritance of the condition seems to be highly responsive to selection pressures of the environment.

In the higher animal phyla, nonhuman porphyrias are either nonexistent, as in the arthropods and urochordates, or rare, as in the various classes of chordates (*2*). The phylogeny suggests a relatively recent origin of the metabolic control mechanism that render the condition a rare disease and not the predominant condition in many species.

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References and Notes

1. G. R. Ruth, S. Schwartz, B. Stephenson, *Science* **198**, 199 (1977).
2. The distribution of porphyrins and references to the older works are given by H. M. Fox and G. Vevers, *The Nature of Animal Colours* (Sidgwick Jackson, London, 1960).
3. The history of this investigation is described by M. L. Laverack, *The Physiology of Earthworms* (Pergamon, Oxford, 1963).
4. G. Y. Kennedy and H. G. Vevers, *J. Mar. Biol. Assoc. U.K.* **32**, 235 (1953); *ibid.* **33**, 663 (1954); G. Y. Kennedy, *ibid.* **35**, 35 (1956); _____ and R. P. Dales, *ibid.* **37**, 15 (1958); G. Y. Kennedy, *ibid.* **38**, 27 (1959).
5. C. P. Mangum and R. P. Dales, *Comp. Biochem. Physiol.* **15**, 237 (1965).
6. C. P. Mangum, in *Adaptation to Environment*, R. C. Newell, Ed. (Butterworth, London, 1976), pp. 225, 231–233.

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Because we are very conscious of the normal accumulation of large amounts of porphyrin in several phyla of multicellular animals (as well as in unicellular organisms, root nodules, and the like), we carefully limited our model comparison with "hereditary human porphyrias" (*1*). The latter have been classified and defined in terms of specific clinical, anatomical, and biochemical manifestations (*2*) which distinguish them from the examples cited by Mangum (*3*). Nonetheless, in a recent report to the NIH, we raised a similar issue, broadening our earlier concepts of hereditary porphyria. Thus, we have now classified the well-known occurrence of protoporphyrin in brown eggshells and uteri of Rhode Island Reds, Japanese quail, and other hens as examples of hereditary uterine porphyria. Similarly, several rodent species exhibit Harderian gland porphyria. A transitory period of normal "physiological" porphyria has been reported in fetuses of many species. Numerous other examples might be cited. We agree that use of the broad term "hereditary porphyria" should be as broad as is its natural normal occurrence, being defined more specifically in each instance in terms of its unique features. The challenge, then, is to determine the special rate-limiting biosynthetic reactions that lead to the porphyrin accumulation and to their possible biochemical and physiological implications, some of which are considered by Mangum.

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References and Notes

1. G. R. Ruth, S. Schwartz, B. Stephenson, *Science* **198**, 199 (1977).
2. U. A. Meyer, in *Progress in Liver Diseases*, H. Popper and F. Schaffner, Eds. (Grune & Stratton, New York, 1976), vol. 5, pp. 280–293; R. Schmid, S. Schwartz, C. J. Watson, *Arch. Intern. Med.* **93**, 167 (1954).
3. C. Mangum, *Science* **201**, 1043 (1978).

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0036-8075/78/0915-1043$00.50/0