lation of the locus coeruleus, the primary source of adrenergic neurons in the central nervous system, can reversibly change the permeability of the brain vasculature to water. Taken together, these functional and anatomical observations lead to the hypothesis that brain capillaries are under neural control. The capillaries might function in a manner similar to other membranes known to regulate water and electrolyte permeability and, as such, contribute to fluid and electrolyte homeostasis of the brain. Our data further support this hypothesis.

Vasopressin reversibly increases brain capillary water permeability when injected into the brain ventricle of the rhesus monkey (*3*). In our study, vasopressin did not affect the cyclic AMP system of brain microvessels in vitro. It is possible that vasopressin acts directly at the capillary by some mechanism unique to brain, which does not involve cyclic AMP. However, the demonstration by Tanaka *et al.* (*12*) that intraventricular vasopressin alters brain norepinephrine turnover in a number of areas, plus the discovery by Swanson (*13*) of an anatomical interconnection between the noradrenergic system and the vasopressin and oxytocin systems in brain, argue for noradrenergic mediation of the vasopressin effect in vivo.

TIMOTHY J. HERBST
MARCUS E. RAICHLE*
JAMES A. FERRENDELLI
Department of Neurology and Neurological Surgery, Washington University School of Medicine, St. Louis, Missouri 63110

References and Notes

1. R. A. Fishman, *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* **53**, 159 (1974).
2. A. Van Harreveld and E. Fifkova, *Exp. Neurol.* **49**, 736 (1975); P. Lipton, *J. Physiol. (London)* **231**, 365 (1973); Y. Y. Geinismann, V. N. Larina, V. N. Mats, *Brain Res.* **26**, 247 (1971).
3. G. P. Haywood and J. Isaia Maetz, *Am. J. Physiol.* **232**, R110 (1977); A. Leaf and R. M. Hayes, *J. Gen. Physiol.* **45**, 921 (1962); E. M. Wright and R. J. Pietras, *J. Membr. Biol.* **17**, 293 (1974); M. Svelto, M. C. R. Perrini, C. Lipps, *ibid.* **36**, 1 (1977). Brain capillaries exhibit a number of anatomical features unique to membranes known to regulate water and electrolyte permeabilities. These include tight junctions between constituent endothelial cells [H. S. Bennett, J. H. Luft, J. C. Hampton, *Am. J. Physiol.* **196**, 381 (1959)]; a high mitochondrial content of constituent endothelial cells [W. H. Oldendorf, M. E. Cornford, W. J. Braun, *Ann. Neurol.* **1**, 409 (1977); compare with W. N. Scott, V. S. Sapirstein, M. Y. Yoder, *Science* **184**, 797 (1974)]; and innervation by adrenergic neurons [B. K. Hartman, D. Zide, S. Udenfriend, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 2722 (1972); M. L. Rennels and E. Nelson, *Am. J. Anat.* **144**, 233 (1975); L. W. Swanson, M. A. Connelly, B. K. Hartman, *Brain Res.* **136**, 166 (1977); T. Itakura, K. Yamamoto, M. Tohyama, N. Shimizu, *Stroke* **8**, 360 (1977); D. M. McDonald and G. L. Rasmussen, *J. Comp. Neurol.* **173**, 475 (1977); T. Iijuma, T. Wasano, T. Tagawa, K. Ando, *Cell Tissue Res.* **179**, 143 (1977); compare with L. Barajar, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **37**, 1192 (1978); J. M. Strum and D. Davon, *Anat. Rec.* **178**, 15 (1974)]. Brain capillaries also exhibit several functional characteristics of membranes which regulate water and electrolyte permeability. These include a restricted permeability to water [M. E. Raichle, J. O. Eichling, M. G. Straatmann, M. J. Welch, K. B. Larson, M. M. Ter-Pogossian, *Am. J. Physiol.* **230**, 543 (1976); compare with N. Bindslev and E. M. Wright, *J. Membr. Biol.* **29**, 289 (1976)]; a prompt increase in water permeability when subjected to an osmotic stress [M. E. Raichle, R. L. Grubb, Jr., J. O. Eichling, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **36**, 470 (1977); compare with N. Bindslev, J. M. Tormey, R. J. Pietras, E. M. Wright, *Biochim. Biophys. Acta* **332**, 286 (1974)]; a change in permeability associated with adrenergic stimulation [M. E. Raichle, B. K. Hartman, J. O. Eichling, L. G. Sharpe, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 3726 (1975); R. L. Grubb, Jr. and M. E. Raichle, *Brain Res.* **144**, 204 (1978); compare with E. Bello-Reuss, D. L. Trevino, C. W. Gottschalk, *J. Clin. Invest.* **57**, 1104 (1976)]; and a change in water permeability produced by vasopressin [M. E. Raichle and R. L. Grubb, Jr., *Brain Res.* **143**, 191 (1978); compare with N. Bindslev, J. M. Tormey, R. J. Pietras, E. M. Wright, *Biochim. Biophys. Acta* **332**, 286 (1974)].
4. F. M. Kregenow, N. E. Robbie, J. Orloff, *Am. J. Physiol.* **231** (No. 2), 306 (1976); T. E. Andreoli and J. A. Schafer, *Annu. Rev. Physiol.* **39**, 451 (1976).
5. G. W. Goldstein, J. S. Wolinsky, J. Csejty, I. Diamond, *J. Neurochem.* **25**, 715 (1975).
6. J. A. Ferrendelli, E. H. Rubin, H. T. Orr, D. A. Inscherf, O. H. Lowry, *Anal. Biochem.* **78**, 252 (1977).
7. O. H. Lowry, N. J. Rosebrough, A. L. Farr, R. J. Randall, *J. Biol. Chem.* **193**, 265 (1951).
8. D. Schlondorff, H. Weber, W. Trigna, L. G. Fine, *Am. J. Physiol.* **234** (No. 1), F16 (1978); R. M. Zusman, H. R. Keiser, J. S. Handler, *J. Clin. Invest.* **60**, 1339 (1977).
9. F. Joo, Z. Rasonczay, M. Wollemann, *Experientia* **3**, 582 (1975).
10. V. Buonassisi and J. C. Venter, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 1612 (1976).
11. R. C. Wagner, P. Kreimer, R. J. Barnett, M. W. Bitensky, *ibid.* **69**, 3175 (1972).
12. M. Tanaka, E. R. de Kloet, D. de Wied, D. H. G. Versteeg, *Life Sci.* **20**, 1799 (1977).
13. L. W. Swanson, *Brain Res.* **128**, 346 (1977).
14. This work was supported by NIH grants NS 09667, NS 11059, and NS 06833.
* Reprint requests to M.E.R. at Division of Radiation Sciences, Edward Mallinckrodt Institute of Radiology, 510 South Kingshighway, St. Louis, Mo. 63110.

7 August 1978; 17 October 1978

Iron Deficiency Prevents Liver Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin

Abstract. *The compound 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) causes hepatocellular damage and porphyria in C57Bl/6J mice, among a wide range of toxic effects. We compared the effect of TCDD toxicity in iron-deficient mice with that in mice receiving a normal diet. Porphyria did not develop in the iron-deficient animals, and these animals were also protected from hepatocellular damage and certain other toxic effects of TCDD.*

The compound 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a potential contaminant of 2,4,5-trichlorophenoxyacetic acid, is extremely toxic to living systems. Pathologic changes in the liver, thymus, skin, and immune system have been reported, and, in addition, TCDD is teratogenic (*1*). This compound causes porphyria cutanea tarda (PCT) in humans and an analogous disturbance of heme synthesis in rats and mice (*2*). More common causes of PCT are alcohol and estrogen therapy. Essentially, this disease comprises light-induced skin damage due to sensitization of the skin by increased concentrations of circulating porphyrin. This porphyrin is predominantly uroporphyrin and a seven-carboxyl porphyrin; it originates in the liver where conversion of uroporphyrinogen to coproporphyrinogen is partially blocked by a decreased activity of uroporphyrinogen decarboxylase (UD). The mechanism whereby TCDD or other hepatotoxins decrease UD is unknown (*3*). As PCT in man may be treated by repeated venesections to reduce body stores of iron (*4*), we designed an experiment to determine whether iron deficiency would protect mice from developing porphyria during exposure to TCDD.

We found that iron deficiency did indeed prevent porphyria, and no decrease in UD was observed in iron-deficient, TCDD-treated mice. However, we found that iron deficiency also protected mice against skin disease caused by TCDD and against liver damage. This was severe in TCDD-treated animals on a normal diet but absent from those animals previously rendered iron-deficient. These results have significance for our understanding of the mechanism of toxicity due to TCDD and related compounds and possibly also for the treatment of TCDD poisoning in man.

We obtained C57Bl/6J mice aged 6 weeks from Jackson Laboratories and fed half either a synthetic iron-deficient diet (*5*) or laboratory chow (*6*). The mice in the group being rendered iron-deficient were anesthetized with ether, and 0.2 to 0.25 ml of blood was withdrawn from the cavernous sinus of each animal twice weekly for 4 weeks; at the end of 4 weeks the hemoglobin concentration had dropped to 5.5 g/dl (*7*). Two of 17 animals died during this preliminary procedure. The iron-deficient diet was maintained; the groups of animals on iron-deficient and regular diets were each subdivided into two groups, treatment and control, and all four groups

0036-8075/79/0420-0332$00.50/0

were separately caged. Treated mice received intraperitoneally 25 μg of TCDD per kilogram of body weight in 0.1 ml of corn oil weekly; control animals received vehicle alone. No further deaths occurred during this experiment. We collected pooled urine samples weekly from each of the four groups of mice over a 24-hour period and measured the total porphyrin spectrophotometrically (*8*).

After 11 weeks of TCDD treatment, the difference between the TCDD-treated mice receiving, respectively, iron-deficient diet and lab chow was well established (Fig. 1). The animals were weighed, photographed, anesthetized with ether, and drained of blood by cardiac puncture. We removed, weighed, and homogenized the liver. A supernatant (the sample was centrifuged at 9000*g* for 20 minutes) was prepared for measurement of mixed function oxygenase (MFO) activity (*9*), UD (*10*), and protein (*11*); a sample was also centrifuged for 60 minutes at 100,000*g* to prepare a microsomal fraction which was used for the determination of cytochromes (*12*), NADPH-cytochrome c reductase (E.C. 1.6.2.4) (*13*), and protein content. Material which could not be assayed immediately was held temporarily in liquid nitrogen. We dissolved a weighed portion of the liver in nitric acid for the determination of iron (*14*), and the tissue was fixed for light microscopy.

In the group of mice being made iron-deficient, the hemoglobin concentration dropped steadily from 10.4 to 5.5 g/dl in pooled blood samples obtained from the cavernous sinus prior to the start of TCDD treatment. However, anemia disappeared during the treatment period despite the continuance of this iron-deficient diet. This result is thought to reflect a redistribution of body iron and a reduced iron requirement with increasing age. Objective evidence for relative iron deficiency in this group was obtained from the reduced total iron in the liver at the end of the 11-week period of TCDD treatment (Table 1). Serum iron was also measured at this time but did not usefully distinguish any two groups.

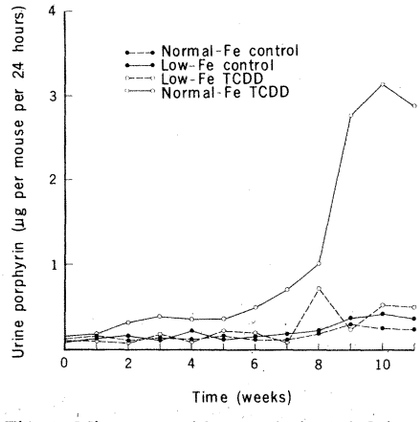

Fig. 1. Mice were either made iron-deficient by repeated blood-letting combined with a synthetic low-iron diet or were fed regular laboratory chow. These two groups were subdivided; either TCDD (25 μg per kilogram of body weight per week) in corn oil or the vehicle alone was given for 11 weeks to mice on the low-iron or regular diet. Pooled urine was collected weekly from each group over a 24-hour period, and the porphyrin content was measured.

Iron-deficient animals did not thrive as well as the group receiving normal amounts of iron, as reflected in reduced body weights when either TCDD-treated or control groups were compared. Nevertheless, the increase in liver weight associated with TCDD treatment was identical (Table 1). This result indicates that liver hypertrophy (of which the induction of hepatic drug-metabolizing enzyme systems by TCDD is a part) occurred in the presence or absence of iron deficiency.

No significant changes in urine porphyrin occurred except in the TCDD-treated group fed regular laboratory diet (Fig. 1). Increases in urine porphyrin in the low-iron, TCDD-treated animals shown at weeks 8, 10, and 11 represented predominantly coproporphyrin, not uroporphyrin as is typical of PCT and the biochemical lesion caused by TCDD. Tissue concentrations of UD were determined when the four groups of animals were killed. The UD activity in the iron-deficient group was 7.99 ± 1.16 units (mean ± standard deviation) in the control group and 7.02 ± 1.65 units in the TCDD-treated group. In the mice receiving regular diet, the UD activity was 6.49 ± 1.16 units in the control group and 1.28 ± 0.79 in the TCDD-treated group, a fivefold decrease; only livers from this group of animals showed red porphyrin fluorescence when inspected in long-wave ultraviolet light. The marked depression of UD was consistent with these findings and contrasts with normal levels of activity of this enzyme in TCDD-treated animals receiving iron-

Table 1. Experimental measurements.

Value	Number of mice*	Hemoglobin† (g/dl)	Body weight (g)	Liver weight (g)	Liver weight (% of body weight)	Total liver iron (μg/g)	Microsomal cytochrome (nmole per milligram of microsomal protein)		NADPH-cytochrome c reductase (μmole per milligram of microsomal protein per minute)	MFO activity‡ (nmole per gram of protein per minute)		
							P-450	b_5		AHH	ERR	7-EC
Iron-deficient diet, control group												
Mean	6	13.4	26.85	1.38	5.17	70.2	0.785	0.350	0.333	5.76	0.220	4.19
S.D.			2.02	0.19	0.80	11.3	0.086	0.047	0.042	1.71	0.034	0.59
Iron-deficient diet, TCDD group												
Mean	9	10.2	23.64	1.9	8.10	86.2	1.44	0.653	0.456	60.42	28.26	24.09
S.D.			1.59	0.27	0.94	5.8	0.137	0.029	0.079	11.01	2.46	3.98
Normal diet, control group												
Mean	7	12.5	33.6	1.72	5.14	121.1	0.727	0.312	0.355	4.09	0.291	3.103
S.D.			2.58	0.23	0.68	9.3	0.131	0.039	0.044	1.24	0.038	0.649
Normal diet, TCDD group												
Mean	10	11.7	30.9	2.34	7.53	144.8	1.727	0.479	0.435	100.12	20.98	24.19
S.D.			3.67	0.35	0.50	11.0	0.132	0.058	0.052	20.42	2.54	2.56

*The experiment commenced with ten animals in each TCDD group to allow for mortality. No deaths occurred, but two mice died during preliminary bleeding. †Hemoglobins were measured on pooled blood samples. ‡AHH, aryl hydrocarbon hydroxylase; ERR, ethoxyresorufin-*O*-de-ethylase; 7-EC, 7-ethoxycoumarin-*O*-de-ethylase; for the methods used, see (*9*). The AHH activity was measured on a 9000*g* supernatant; ERR and 7-EC activities were measured on microsomal fractions.

deficient diet, thus disproving a direct effect of TCDD on UD.

The protection of the livers of these mice from pathologic changes produced by TCDD also appears to have been complete in the iron-deficient group. Apart from differences in weight, none of the livers presented obvious macroscopic differences. Microscopically, however, changes were striking in one group, and appearances were consistent in all animals within the same group. The TCDD-treated animals on regular laboratory diet showed a severe degree of disarray of the hepatic lobular architecture due to swelling of the parenchymal cells. Cytoplasm was markedly vacuolated, and this change was more marked in the mid and peripheral zone of the lobules (Fig. 2A). The central area showed a striking eosinophilia of the cytoplasm, and throughout the lobule there were focal areas of individual cell necrosis with an associated mononuclear inflammatory cell infiltrate. Reticuloendothelial elements (Kupffer cells) were prominent and an increase in reticulin fibers was noted, particularly in and around the portal tracts. No fat was demonstrated, and stainable iron was absent. In contrast, the livers of TCDD-treated animals fed iron-deficient diet were normal histologically (Fig. 2B) except for an increase in cytoplasmic eosinophilic material, consistent with hypertrophic smooth endoplasmic reticulum. Livers of control animals showed no abnormality.

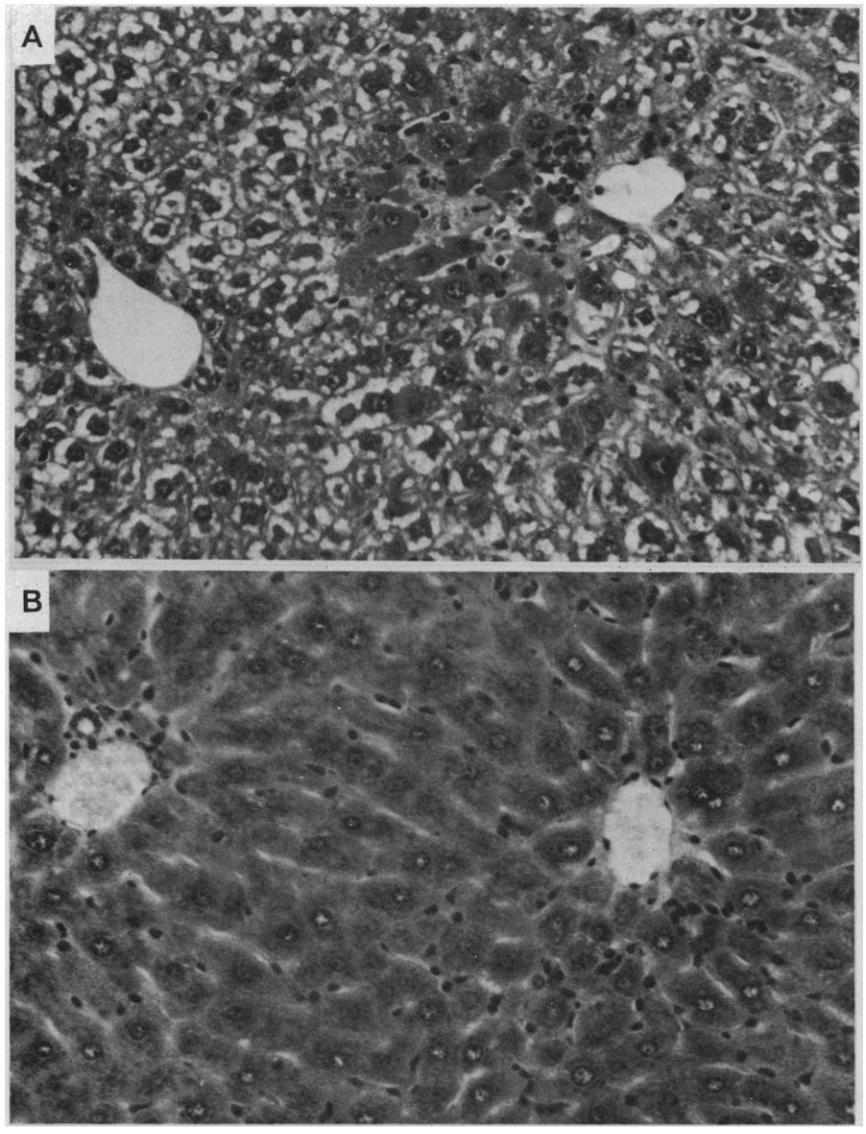

Fig. 2. Four groups of mice, on a regular or low-iron diet and receiving injections of TCDD in vehicle or vehicle only, were prepared as described in Fig. 1. After the mice had been killed, portions of the liver were fixed in Carnoy's fluid, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin. Magnification, ×285. (A) Micrograph demonstrating the effect of TCDD on mice consuming the regular diet. There is some loss of lobular architecture, extensive vacuolization of the cytoplasm in the peripheral zone, and centrilobular cell necrosis. (B) Micrograph of liver tissue from a TCDD-treated, iron-deficient animal. Apart from some increase in acidophilic cytoplasm consistent with hypertrophic smooth endoplasmic reticulum, the section is normal. Within groups, it was not possible to distinguish any significant differences in liver morphology.

The pathogenesis of TCDD-induced porphyria is not understood. In earlier work, we have compared mice that were, or were not, genetically resistant to the induction of hepatic microsomal cytochrome by TCDD (*15*). We showed that 25 μg of TCDD per kilogram of body weight per week only decreased UD activity and caused porphyria in the strain more susceptible to the induction of cytochrome P-448 and aryl hydrocarbon hydroxylase (AHH) by TCDD.

More detailed information on the activity of hepatic MFO systems is therefore given in Table 1. Cytochrome P-450 activity was higher in the group receiving normal amounts of iron, but the difference was not significant. The MFO activity was variable depending upon the substrate used: *O*-de-ethylation of ethoxyresorufin and 7-ethoxycoumarin was comparable in the two groups, but the conversion of benzpyrene to fluorescent products (AHH) showed greater stimulation by TCDD in the group receiving normal amounts of iron. This difference was not statistically significant ($P = .2$), but we cannot conclude that hepatic MFO systems were equally induced by TCDD treatment in both normal and iron-deficient groups of mice.

The general condition of the TCDD-treated animals receiving normal diet deteriorated progressively. The hair grayed, bald patches appeared over the animals' backs, and the fur was neglected. None of these signs were noted in the iron-deficient animals treated with TCDD (these animals were indistinguishable from either set of control animals except for their smaller size).

Two explanations for the protection afforded against TCDD toxicity by iron deficiency may be considered. Possibly there was not enough iron to permit the induction of hemoproteins such as cytochrome P-448 that play an essential role in the toxicity of TCDD, but we have little evidence to support this. (i) At the end of the experiment, the mice were not notably anemic. (ii) Liver hypertrophy due to TCDD was not significantly different in the normal-iron and iron-deficient groups. (iii) The induction of MFO activity was comparable. Alternatively, tissue iron in some other form

plays an essential role in the toxic changes induced by TCDD. We favor this explanation, which is also consistent with reversal of the biochemical disturbance of PCT in man by venesection. In addition, reversal by repeated venesection of cirrhosis apparently caused by hepatocellular iron deposits has been reported (*16*).

These results have far-reaching significance. First, they demonstrate synergism between a normal concentration of dietary iron in laboratory animals and the specific toxin TCDD. Second, the toxic effects of TCDD are not unique to this molecule. Although TCDD may be the most potent of this class of MFO-inducing agents, the difference may only be quantitative; polychlorinated biphenyls demonstrate similar effects, and Poland and Glover have shown (*17*) that polychlorinated and polybrominated biphenyls with halogen atoms in the appropriate positions closely resemble TCDD as inducers of AHH and heme synthesis.

G. D. SWEENEY, K. G. JONES
F. M. COLE, D. BASFORD
F. KRESTYNSKI

Departments of Medicine, Biochemistry, and Pathology, McMaster University, Hamilton, Ontario, L8S 4J9 Canada

References and Notes

1. D. Neubert, P. Zens, A. Rothenwallner, H. J. Merker, *Environ. Health Perspect.* **5**, 67 (1973); B. A. Schwetz, J. M. Norris, G. L. Sparschu, V. K. Rowe, P. J. Gehring, J. L. Emerson, C. G. Gerbig, *ibid.*, p. 87; M. W. Harris, J. A. Moore, J. G. Vos, B. N. Gupta, *ibid.*, p. 101; B. N. Gupta, J. G. Vos, J. A. Moore, J. G. Zinkl, B. C. Bullock, *ibid.*, p. 125; J. G. Vos, J. A. Moore, J. G. Zinkl, *ibid.*, p. 149.
2. J. Bleiberg, M. Wallen, R. Brodkin, I. Applebaum, *Arch. Dermatol.* **89**, 793 (1964); J. A. Goldstein, P. Hickman, H. Bergman, J. G. Vos, *Res. Commun. Chem. Pathol. Pharmacol.* **6**, 919 (1973).
3. U. A. Meyer and R. Schmid, in *The Metabolic Basis of Inherited Disease*, J. B. Stanbury, J. B. Wyngaarden, D. S. Fredrickson, Eds. (McGraw-Hill, New York, 1978), p. 1166.
4. H. Ippen, *Panminerva Med.* **4**, 381 (1962).
5. Nutritional Biochemicals powdered low-iron diet (catalog number 902199) was moistened, baked into slabs at 90°C overnight, and then broken into chunks suitable for mice. No iron could be detected by means of a colorimetric assay sensitive to 0.25 part per million of iron (*14*).
6. Teklad mouse-rat diet (6 percent fat). The calculated iron content of this diet was 0.013 percent (Teklad Test Diets, Box 4220, Madison, Wis.). We measured the total iron after digestion in nitric acid and found 0.07 percent. The bioavailability of this iron is unknown.
7. Blood samples withdrawn were pooled and hemoglobin was determined in duplicate as cyanmethemoglobin [D. L. Drabkin and J. H. Austin, *J. Biol. Chem.* **112**, 51 (1935)].
8. K. G. Jones and G. D. Sweeney, *Biochem. Med.* **15**, 223 (1976).
9. We measured the MFO activity, using three reactions dependent upon cytochrome P-450 (P-448) systems. The AHH was assayed as previously described [G. D. Sweeney, R. E. Garfield, K. G. Jones, A. N. Latham, *J. Lab. Clin. Med.* **91**, 432 (1978)]. We measured 7-ethoxycoumarin-*O*-de-ethylase according to the method of V. Ullrich and P. Weber [*Hoppe-Seyler's Z. Physiol. Chem.* **353**, 1171 (1972)]. For the measurement of ethoxyresorufin-*O*-de-ethylase, we followed the method of M. D. Burke and R. T. Mayer [*Drug Metab. Dispos.* **2**, 583 (1974)].
10. The assay for UD (*15*) was modified from the method of G. H. Elder [*Clin. Sci. Mol. Med.* **51**, 71 (1976)]. Units of activity are nanomoles of coproporphyrinogen formed per gram of liver per minute.
11. E. W. Sutherland, C. F. Cori, R. Haynes, N. S. Olsen, *J. Biol. Chem.* **180**, 825 (1949).
12. T. Omura and R. Sato, *ibid.* **239**, 2370 (1964).
13. C. H. Williams and H. Kamin, *ibid.* **237**, 587 (1962); NADPH, reduced form of nicotinamide adenine dinucleotide phosphate.
14. Liver or diet was digested in boiling nitric acid on a sand bath and filtered; the iron was determined colorimetrically with sulfonated bathophenanthroline [R. J. Henry, *Clinical Chemistry: Principles and Technics* (Hoeber, New York, 1964), chapter 14, p. 387].
15. K. G. Jones and G. D. Sweeney, *Res. Commun. Chem. Pathol. Pharmacol.* **17**, 631 (1977).
16. M. S. Wheby, paper presented at the 18th annual meeting of the American Society for Clinical Nutrition, San Francisco, Calif., April 1978, abstract 721; J. P. Weill, M. Weill-Bousson, R. Baumann, A. Kerschen, paper presented at the World Congress on Gastroenterology, Madrid, June 1978, abstract 177.
17. A. Poland and E. Glover, *Mol. Pharmacol.* **13**, 924 (1977).
18. This work was supported by the Medical Research Council of Canada. We thank M. Jackson for help in the preparation of this manuscript.

20 September 1978; revised 22 January 1979

A Theory of Diversity Equilibrium and Morphological Evolution

Abstract. *If the world can only support a finite amount of biomass, species might be added over time, with a decrease in population size of an average species. Population sizes of species will decrease to the extent that stochastic events eliminate species as fast as others appear, yielding an equilibrium. A resource diversity control of niche subdivision is therefore not needed to generate an equilibrium number of species. Morphological evolution may decelerate over time for similar reasons.*

Several paleontologists have characterized evolutionary diversification as a balance between speciation and extinction rates (*1*). The establishment of an evolutionary equilibrium between speciation and extinction due to area effects has been suggested by some workers (*2*), and the control of resource limitation on the upper limit of species number has been suggested by others (*3*). Both approaches predict an equilibrium number of coexisting species, and Sepkoski (*4*) has developed the mechanics of a logistic model of species addition. Whatever the mechanism, some evidence suggests that taxon richness can remain constant over long periods of geologic history. Taxon equilibria have been suggested for the entire shallow water marine biota as well as for species richness within a single fossil sedimentary basin (*4*, *5*). I here provide a model with a minimal number of assumptions to account for an equilibrium.

Consider an unchanging world in which competitive interactions set no limit on the maximum number of coexisting species. Also assume that regardless of species richness, S, the total number of individuals is limited, simply because the world can hold only so much biomass. If both these assumptions are true, then the species present at any one time have a mean individual species population size, $\bar{P}$, with some undefined distribution about the mean. The more species present, the smaller is the mean population size per species. Under this scheme, resource utilization is mainly established by priority. We can imagine such a case for marine epibenthic invertebrates, where space limits the total number of individuals.

Next assume a rate of diversification for a given taxonomic group that is at first positive and constant. The value of this rate should depend on the adaptive mode, reproductive type, and degree of social organization (*6*). However, a species evolving into a biota that has many species will of necessity attain a probabilistically smaller population size than when few species are present. We cannot predict what population size a specific newly evolved species will attain. Given the above assumptions, there is a critical lower value of $\bar{P}$, $\bar{P}_c$, below which more species will become extinct than appear. With an upper limit to the total number of individuals, the addition of new species will bring $\bar{P}$ below the level that the rarest species are likely to survive random events causing population decline. These events might be disease, invasion of parasites, competitive displacement by neighboring species, or a short-term climatic change that disrupts reproduction. When $\bar{P} > \bar{P}_c$, the addition of species will not have this effect. If species richness is minimal, immigration from outside areas can depress local extinction. There is a corresponding species richness, S_c, which is the equilibrium point. The ratio S/S_c might indicate the factor by which speciation success can be gauged, as suggested by Sepkoski (*4*).

We can imagine an adaptive radiation in the context of this model. When a new taxonomic type appears and as S approaches S_c, the proportional survival of newly proliferated species will decrease as $\bar{P}$ approaches $\bar{P}_c$. Overshoots and oscillations could be imagined, but an evolutionary equilibrium can be attained

0036-8075/79/0420-0335$00.50/0