

be responsible for the large observed changes of T_m and might explain the role of the lactones in the activity of the AM molecule.

It seems appropriate to consider the possibility that the invariable restricted distribution of DNA functional groups might underlie the enzymatic specificity of the nucleic acid polymerases. All available evidence concerning the activity of these enzymes points to the likelihood that the replication of templates occurs by way of a mechanism in which sequences are determined by the type of base pairing which occurs in DNA. If this is the case, the hydrogen-bonding system of the native helix would have to be disrupted, at least at the site of enzyme action. The hydrogen bonds linking the base pairs are centrally located around the helix axis; and the hydrogen bonds between any base pair could be severed by an enzymatic approach from either groove. Denaturation of a short segment would allow the affected bases to rotate, permitting normal base pairing with incoming nucleotides to occur in either groove. It may be significant that proflavine, which is thought to intercalate between successive base pairs (26), thus affecting the structure of both DNA grooves, inhibits both nucleic acid polymerases unselectively (3, 5), whereas AM, which is assumed to bind only in the minor groove (9), exhibits striking selectivity in its effect on the same enzymes. Therefore, it seems reasonable to propose, as a working hypothesis, that each nucleic acid polymerase normally "sees" the DNA base sequence from only one groove. RNA-polymerase is displaced from DNA by AM (30). If AM is assumed to lie in the minor groove, it would seem logical to expect that this groove is the specific template site for RNA-polymerase and thus the site of RNA synthesis and perhaps of its regulation. DNA replication would then be postulated to proceed in the major groove. These possibilities can be tested experimentally.

E. REICH

Rockefeller Institute, New York 21

References and Notes

1. I. J. Slotnick, *Ann. N.Y. Acad. Sci.* **89**, 342 (1960); J. M. Kirk, *Biochim. Biophys. Acta* **42**, 167 (1960).
2. E. Reich, R. M. Franklin, A. J. Shatkin, E. L. Tatum, *Science* **134**, 556 (1961); *Proc. Natl. Acad. Sci. U.S.* **48**, 1238 (1962).
3. I. H. Goldberg and M. Rabinowitz, *Science* **136**, 315 (1962).
4. G. Hartmann and U. Coy, *Angew. Chem.* **74**, 501 (1962); G. Hartmann, U. Coy, G. Kniese, *Z. Physiol. Chem.* **330**, 227 (1962).
5. J. Hurwitz, J. J. Furth, M. Malamy, M. Alexander, *Proc. Natl. Acad. Sci. U.S.* **48**, 1222 (1962).
6. E. Reich, I. H. Goldberg, M. Rabinowitz, *Nature* **196**, 743 (1962).
7. I. H. Goldberg, M. Rabinowitz, E. Reich, *Proc. Natl. Acad. Sci. U.S.* **48**, 2094 (1962); *ibid.* **49**, 226 (1963).
8. E. Kahan, F. Kahan, J. Hurwitz, *J. Biol. Chem.* **238**, 2491 (1963).
9. L. Hamilton, W. Fuller, E. Reich, *Nature* **198**, 538 (1963).
10. W. Müller, *Naturwiss.* **49**, 156 (1962).
11. H. Brockmann, *Fortschr. Chem. Org. Naturstoffe* **18**, 1 (1960).
12. E. Reich, unpublished observations.
13. H. Muxfeldt, personal communication.
14. W. Kersten, *Biochim. Biophys. Acta* **47**, 610 (1961).
15. R. Langridge, D. Marvin, W. Leeds, H. Wilson, C. Hooper, M. Wilkins, L. Hamilton, *J. Mol. Biol.* **2**, 38 (1960).
16. W. Müller, personal communication.
17. M. Gellert, M. Lipsett, D. Davies, *Proc. Natl. Acad. Sci. U.S.* **48**, 2013 (1962).
18. L. Lerman, personal communication.
19. J. D. Leith, Jr., *Biochim. Biophys. Acta* **72**, 643 (1963).
20. M. Izawa, V. Allfrey, A. E. Mirsky, *Proc. Natl. Acad. Sci. U.S.* **49**, 544 (1963).
21. R. Haselkorn, *Science*, this issue.
22. R. L. Sinsheimer, *J. Mol. Biol.* **1**, 43 (1959).
23. H. K. Schachman, J. Adler, C. M. Radding, I. R. Lehman, A. Kornberg, *J. Biol. Chem.* **235**, 3242 (1960).
24. E. Reich and I. H. Goldberg, in preparation.
25. W. Kersten and H. Kersten, *Z. Physiol. Chem.* **330**, 21 (1962).
26. L. S. Lerman, *J. Mol. Biol.* **3**, 18 (1961).
27. S. R. Kornberg, S. Zimmerman, A. Kornberg, *J. Biol. Chem.* **236**, 1487 (1961).
28. A. Kornberg, *Enzymatic Synthesis of DNA* (Wiley, New York, 1961).
29. C. M. Radding, J. Josse, A. Kornberg, *J. Biol. Chem.* **237**, 2869 (1962).
30. I. H. Goldberg, E. Reich, M. Rabinowitz, *Nature* **199**, 44 (1963).
31. M. Chamberlin and P. Berg, *Proc. Natl. Acad. Sci. U.S.* **48**, 81 (1962).
32. I. R. Lehman, M. J. Bessman, E. S. Simons, A. Kornberg, *J. Biol. Chem.* **233**, 163 (1958).
33. I thank E. L. Tatum for encouragement; A. Kornberg and R. Inman for dIdC; M. Roger for pneumococcal DNA; D. L. Hamilton for *N*-dimethylene actinomycin; S. Huang for a sample of DNA-polymerase; H. Moroson for the use of a Beckman spectrophotometer; W. Fuller and R. Haselkorn for helpful discussion, and the Helen Hay Whitney Foundation and National Institutes of Health for support.

15 November 1963

Diabetes Mellitus in the Sand Rat Induced by Standard Laboratory Diets

Abstract. During an attempt to establish a laboratory colony of the sand rat (*Psammomys obesus*) we found that this animal invariably became obese and developed severe diabetes mellitus when fed on commercial laboratory rat feed, but remained normal when fed on fresh vegetables only. The signs of diabetes included elevated blood glucose, excessive glucose and ketone bodies in the urine, and cataracts. The diabetic animals showed degeneration of the pancreatic insulin-producing tissue (beta-cells).

The North African rodent *Psammomys obesus*, or the sand rat, inhabits areas where the vegetation consists of fleshly salt-loving plants (for example, *Salicornia*). The sand rat seems to eat exclusively these succulent plants in which the sap has a salt content often in excess of that in sea water (1). Our interest in establishing a laboratory colony of sand rats was based on their exceptional tolerance to salt and the high concentrating capacity of their kidneys.

Adult sand rats imported from Egypt were mated in the laboratory and produced seemingly normal litters. The young grew well until weaning but soon afterward developed cataracts and during the following months most of them died. There was seldom any outward indication of the reason for death, and there was no general infection, except in cases where a wound or broken tooth was present. We did record, however, that one or more of the following signs of diabetes mellitus existed in approximately 60 of these laboratory-reared sand rats: cataracts, elevated

blood and urine sugar, ketonuria, and degeneration of the pancreatic beta-cells as shown by aldehyde-fuchsin staining.

The animals were fed on a standard laboratory diet (Purina Laboratory Chow), supplemented with occasional carrots; either water or a 5-percent NaCl solution was provided for drinking. To discover possible nutritional deficiencies we supplemented the usual diet of certain animals with various combinations of the following additives: salts and trace elements, the common vitamins, increased protein, and liberal amounts of fresh vegetables (2). Mixed grains (cracked corn, oats, millet, and sorghum) were provided, either alone or in addition to the usual diet, to some of the sand rats so that preferred items might be selected. None of these various nutritional measures improved the condition of the animals. It then appeared reasonable that the signs we had observed were caused either by the standard laboratory diet (or some dry, high-energy food such as the mixed grains) or they re-

Table 1. Evidence of diabetes mellitus in sand rats (*Psammomys obesus*).

Sex	Age (mo)	Wt. (g)	Glucose (mg/100 ml)		Age when cataracts observed (mo)	Pancreas		Glycogen nephrosis
			Plasma	Urine		Beta-cell degranul.	Vacuoles	
Diet: Laboratory chow and vegetables								
♀	6	221.5	565	12,700	2	++++	+++	+++
♀	7	219.0	560	20,700	4	++++	+++	+++
♀	6	218.0	498	15,600	3	++++	+++	+++
♂	7	258.3	489	9,700	3	++++	+++	+++
♂	7	223.0	466	9,030	2	++++	+++	+++
♂	7	317.5	386	9,320	2	++++	+++++	+++
♂	6	238.0	268	3,880	3	++++	0	0
♀	7	310.5	192	38	4	+++	0	0
♀	7	291.8	140	84	—	++++	0	0
♂	7	274.0	140	2.5	4	++++	+	0
♀	6	217.0	110	65	5	+++	0	0
♀	7	225.0	70	122	4	0	0	0
Diet: Vegetables								
♀	9	141.5	117	84	—	0	0	0
♂	9	169.0	94	59	—	0	0	0
♀	9	128.0	94	8.1	—	0	0	0
♀	7	93.5	62	3.1	—	0	0	0
♂	9	152.9	59	0.8	—	0	0	0

flected a high incidence of naturally occurring diabetes in this species.

In order to evaluate this latter possibility, animals freshly trapped in Egypt were examined immediately. In 40 animals the mean plasma glucose concentration was 97.8 ± 7.35 mg/100 ml (S.E.), and in 36 animals the mean urine glucose concentration was 15.1 ± 1.90 mg/100 ml. In all these animals the pancreas was histologically normal and contained well-developed islet structures with normal beta-cells. Thus, diabetes does not seem to occur in sand rats in the wild state.

The hypothesis that the diabetes was caused by the diet provided in the laboratory was tested by keeping female sand rats with their newborn young on two different diets and then raising the young on these diets after weaning. One group (12 young) received Purina Laboratory Chow (49.4 percent digestible carbohydrate, 23.4 percent protein, and 3.8 percent fat) as desired, supplemented with fresh mixed vegetables (carrots, beets, beet greens, and spinach); the other group (10 young) received fresh mixed vegetables only, as desired. Five of the ten animals fed vegetables were killed for histological examination. Water was available to all the animals. Samples of blood and urine were collected and analyzed for glucose at monthly intervals from the time of birth until the experiment was terminated.

The 12 animals feeding on laboratory chow began to develop cataracts and elevated urine sugar at the age of 2 months, and when the experiment was terminated at 6 to 7 months 11 of these

animals had cataracts (Table 1). The beta-cells of the islets of Langerhans showed marked degranulation in sections stained with aldehyde-fuchsin. The only animal in this group with normal beta-cell granulation also had a normal concentration of plasma glucose. The six animals with the highest concentration of glucose in urine and plasma showed marked vacuolar changes of the islet cells and glycogen nephrosis. The five animals fed on vegetables only were carried to an age of 9 months to permit time for development of any incipient diabetes (one died of pneumonia at seven months). However, none of this group had cataracts, all had normal pancreatic islets, the plasma glucose was in a normal range, and although glucose was occasionally found in the urine it was always relatively low. The animals feeding on laboratory chow were quite obese (body weight, 251.1 ± 11.0 g

S.E.) while those on vegetables (148.0 ± 8.6 g) were in the range of animals trapped in nature (141.4 ± 10.7 g).

The only rodent in which spontaneous diabetes mellitus has been reported is an inbred strain of the Chinese hamster (3). The diabetes mellitus that occurs in the Egyptian sand rat is of particular interest since in many respects it resembles the clinical and pathologic picture of human diabetes. Because the onset of the disease in the sand rat can be strictly controlled by the type of diet fed, this animal should be an excellent experimental model with which to study the interrelations of such factors as diet, obesity, and early metabolic and pathologic changes.

At the present time the cause of the diabetes that occurs in the sand rat is not known, although it may be due to an excessive caloric intake, or to a carbohydrate intake that is greater than that occurring in the natural diet.

KNUT SCHMIDT-NIELSEN

HOWARD B. HAINES

DONALD B. HACKEL

Departments of Zoology and
Pathology, Duke University,
Durham, North Carolina

References and Notes

1. K. Schmidt-Nielsen, *Desert Animals. Physiological Problems of Heat and Water* (Clarendon Press, Oxford, England, 1964).
2. The mineral mixture used was that of A. C. Harper, *J. Nutrition* **68**, 408 (1959). Pastes of brewer's yeast and dry milk provided additional protein and water soluble vitamins. Wheat germ oil was used as a source of fat soluble vitamins.
3. H. Meier and G. Yerganian, *Proc. Soc. Exptl. Biol. Med.*, **100**, 810 (1959).
4. The original stock of sand rats was generously provided by H. Hoogstraal, U.S. Naval Medical Research Unit No. 3, Cairo, Egypt. This work was supported by NIH grant HE-02228 and was done during the tenures of a NIH postdoctoral fellowship No. GPD-14,316-C1 to one of us (H.B.H.), and a U.S. Public Health Service Career Research Award to another (D.B.H.).

15 November 1963

Water Transport across Root Cell Membranes:

Effect of Alkenylsuccinic Acids

Abstract. *Alkenylsuccinic acids increase permeability of cells to water by incorporation of the molecules into the lipid layer of the cytoplasmic membrane, thereby changing the membrane from a phase characterized by a high activation energy for water transport to a phase where only the effect of the viscosity of water is observable.*

Currier (1) observed a sudden increase in permeability of plant cells exposed to benzene vapor, which he ascribed to the destruction of the lipid-rich plasma membrane. Similar effects

of ether and chloroform have been described by Chibnall (2). Van Overbeek and Blondeau (3) concluded from their experiments that phytotoxic hydrocarbons are taken up by the cell membrane