Technical Papers

Effect of ACTH and Some Adrenocortical Steroids on the Metabolism of Tyrosine and Phenylalanine in Premature Infants[1]

S. Z. Levine, Henry L. Barnett, C. Warren Bierman,[2] and Helen McNamara

Department of Pediatrics, The New York Hospital–Cornell Medical Center, New York

In 1939, Levine *et al.* (*1–4*) found that premature infants receiving high-protein diets devoid of vitamin C had a specific defect in metabolism of tyrosine and phenylalanine manifested by urinary excretion of the tyrosyl derivatives *p*-hydroxyphenylpyruvic acid and 1-*p*-hydroxyphenyllactic acid. Without exception, administration of ascorbic acid promptly abolished the defect (*5*). In subsequent investigations, although some substances, including crude liver extract (*5, 6*), folic acid, and vitamin B_{12} (*6, 7*), were partly or inconsistently effective, no agent other than ascorbic acid consistently corrected the tyrosyluria of premature infants.

The important role of vitamin C in aromatic amino acid metabolism has also been demonstrated in infants (*8*) and adults (*9*) with latent and manifest scurvy. Investigation was extended to scorbutic and nonscorbutic guinea pigs by means of *in vivo* studies (*10*) and *in vitro* enzymatic experiments with liver substrates (*11–13*). In this species, also, the metabolic defect developed and was promptly corrected by ascorbic acid. Folic acid was much more consistently effective in the guinea pig than in the premature infant (*14*).

An interrelationship between ascorbic acid and adrenocortical function has long been recognized. Ascorbic acid has been shown to be present in adrenal and pituitary glands in much higher concentrations than in most other body tissues (*15–17*). A prompt fall of ascorbic concentration in the adrenal gland (*17, 18*) occurs in conditions of acute stress and has also been produced by administration of pituitary adrenocorticotropic hormone to animals. No such lowering of ascorbic acid content takes place in other tissues (*17*). These facts prompted the present studies of the effect of ACTH and of adrenal hormones on tyrosyluria of premature infants.

To determine the effect of ACTH and the various steroids[3] on the tyrosyluria of premature infants on a high-protein ascorbic acid-free diet, 17 infants were given ACTH in 24 observations. Six infants received cortisone in 8 observations, 2 desoxycorticosterone acetate, 1 dehydrocorticosterone, and 1 Reichstein's Compound "L" (*19*) in varying dosages intramuscularly and usually at 3- or 6-hr intervals. Three other infants were given progesterone, and 2 received testosterone. Casual specimens of urine were analyzed daily for tyrosyl derivatives by methods described in a previous communication (*2*).

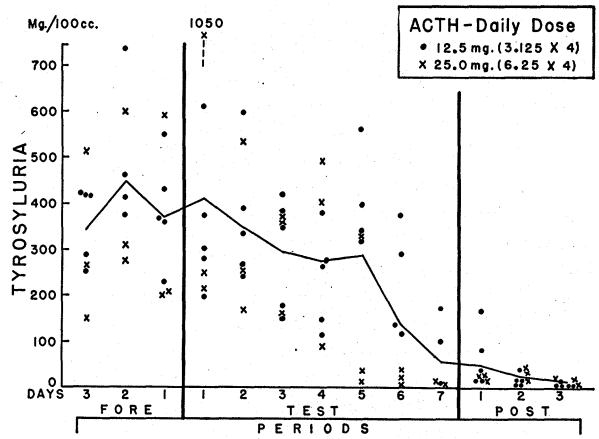

FIG. 1. Effect of ACTH on tyrosyluria of premature infants.

The tyrosyluria was corrected in all of 19 observations on 17 premature infants, male and female, white and colored, in which ACTH was given for 3 or more days in a total dosage exceeding 60 mg. Fig. 1 shows the responses in 8 infants who received 12.5–25 mg of ACTH daily for 7 days. Tyrosyluria was not abolished more quickly in 9 infants who received 50 mg during similar periods.

Larger doses given during shorter periods (100 mg for 1 day and 200 mg over a 2-day period) proved unsuccessful. In one infant, 48 mg over a 3½-day period produced no change in tyrosyluria, but 60 mg over a 5-day period resulted in its disappearance. In none of the infants treated with ACTH did the tyrosyl compounds disappear earlier than the fifth day after onset of treatment. These results indicate that tyrosyluria responds much less promptly to ACTH than to ascorbic acid, and, furthermore, that a certain minimum duration of therapy is required. In contrast an adequate dose of vitamin C abolishes tyrosyluria in 24–48 hr.

It may reasonably be assumed that ACTH abolishes the metabolic defect by stimulating the secretion of one or more of the adrenal hormones; for this reason, the effect of several individual steroids was investigated. Desoxycorticosterone (up to 15 mg in 5 days), dehydrocorticosterone (750 mg in 7 days), Reichstein's Compound "L" (700 mg in 7 days), progester-

[1] This investigation was aided by a grant from the Playtex Park Research Institute.

[2] Supported by a fellowship from the National Foundation for Infantile Paralysis.

[3] We are indebted to the following persons and institutions for the various preparations used in this study: Cornelius P. Rhodes and Konrad Dobriner, Sloan-Kettering Institute, for dehydrocorticosterone (Merck); Edward W. Henderson, Schering Corporation, for progesterone; and Irvin V. Sollins, Chemical Specialties Co., Inc., for Compound "L" of Reichstein.

one (up to 700 mg in 7 days), and testosterone (up to 70 mg in 7 days) all were ineffective in the relatively large doses employed. Further study of these and related compounds is planned.

Results with cortisone were inconsistent. Total doses of at least 350 mg during 3½ days or more were effective in 3 observations, whereas 2 infants receiving relatively larger doses (100 mg daily for at least 7 days) failed to respond. Total dosages of less than 350 mg were ineffective in 3 cases. The failure of these large doses of cortisone to correct the defect in 5 of 8 observations needs further investigation.

ACTH given in adequate dosage over a sufficient period of time abolishes the defect in aromatic amino acid metabolism manifested by premature infants receiving high-protein diets deficient in ascorbic acid. The mechanism by which ACTH arrests tyrosyluria while concomitantly altering protein metabolism remains obscure. The correction would not seem to involve mobilization of stored ascorbic acid as suggested by the fact that in 2 infants no change in plasma or white blood cell ascorbic acid concentration and no increase in urinary ascorbic acid excretion occurred during therapy. ACTH differs from ascorbic acid in that more prolonged administration is necessary. Moreover, ACTH did not prevent development of the defect in 1 infant so studied, whereas adequate ascorbic acid administration prevents the occurrence of tyrosyluria (*5*).

These data indicate, therefore, that tyrosyluria resulting from an ascorbic acid-free, high-protein diet in premature infants can be consistently abolished by ACTH, inconsistently by cortisone, and is apparently uneffected by desoxycorticosterone, dehydrocorticosterone, Compound "L" of Reichstein, progesterone, or testosterone. One hundred mg of cortisone per day does not as uniformly eliminate tyrosyluria as does ACTH in a dose of only 12.5 mg per day. This suggests either that ACTH stimulates the premature adrenal to elaborate surprisingly large quantities of cortisone or that it increases the secretion of one or more other adrenocortical hormones which either act alone or together with cortisone to correct the tyrosyluria.

References

1. LEVINE, S. Z., MARPLES, E., and GORDON, H. H. *Science,* **90**, 620 (1939).
2. ———. *J. Clin. Invest.*, **20**, 199 (1941).
3. LEVINE, S. Z., DANN, M., and MARPLES, E. *Ibid.*, **22**, 551 (1943).
4. LEVINE, S. Z. *Harvey Lectures, Ser. 42* (1946–47), 303.
5. LEVINE, S. Z., GORDON, H. H., and MARPLES, E. *J. Clin. Invest.*, **20**, 209 (1941).
6. GOVAN, C. D., JR., and GORDON, H. H. Presented at Society for Pediatric Research, May 3–4, 1949.
7. ———. *Science,* **109**, 332 (1949).
8. MORRIS, J. E., HARPUR, E. R., and GOLDBLOOM, A. *J. Clin. Invest.*, **29**, 325 (1950).
9. ROGERS, W. F., JR., and GARDNER, F. *Ibid.*, **28**, 806 (1949).
10. SEALOCK, R. R., and SILBERSTEIN, H. E. *J. Biol. Chem.*, **135**, 251 (1940).
11. LAN, T. H., and SEALOCK, R. R. *Ibid.*, **155**, 483 (1944).
12. SEALOCK, R. R., and GOODLAND, R. L. *Ibid.*, **178**, 939 (1949).
13. RIENITS, K. *Ibid.*, **182**, 11 (1950).
14. WOODRUFF, C. W., *et al. Ibid.*, **178**, 861 (1949).
15. SAMUELS, L. T. *J. Nutrition,* **36**, 205 (1948).
16. HARTMAN, F. A., and BROWNELL, K. A. *The Adrenal Gland.* Philadelphia: Lea & Febiger, 285 (1949).
17. SAYERS, G., *et al. Endocrinology,* **37**, 96 (1945).
18. SAYERS, G., *et al. Proc. Soc. Exptl. Biol. Med.,* **55**, 238 (1944).
19. REICHSTEIN, T., and SHOPPEE, C. W. *Vitamins and Hormones,* Vol. 1. New York: Academic Press, 364 (1943).

Motion in the Solar Atmosphere as Deduced from Radio Measurements

Grote Reber

Radio Division,
National Bureau of Standards, Washington, D. C.

It is known that an appreciable amount of ionization exists in the atmosphere of the sun whose pressure decreases at increasing heights above the photosphere. Thus, the value of the electron density is a decreasing function of height in the solar atmosphere. Theoretical considerations (*1*) indicate that when two charged plasmas, of commensurate charge density, are allowed to mix, some of the energy of motion will be converted into electromagnetic energy at the interface of motion. The frequency of maximum radiated energy will be dependent primarily upon the charge density. The intensity of the energy radiated will depend primarily upon the vigor of the relative motion and the sharpness of the interface of motion in terms of wavelengths. It is therefore apparent that turbulence in the solar atmosphere should generate radio waves of a transient nature. Recourse to measurement by suitable equipment shows that the expectations are amply verified. In fact, the profusion of effects is so great, and the types so varied at different times and frequencies, that the observer is hard put to it to learn the fundamentals of the phenomena being studied.

Owing to the ionization in the solar atmosphere, only high frequencies can escape from the lower levels, whereas conditions in the outer parts of the atmosphere favor the generation of lower frequencies. Accordingly, to a first approximation, we may consider that different radio frequencies are generated at different levels in the solar atmosphere. The microwaves should come from near the photosphere. The decameter waves will probably be generated in the outer parts of the corona. It is apparent that if a projectile were to be ejected from the photosphere it would stir up and cause turbulence in various layers of the solar atmosphere consecutively. Thus, it should be possible to detect the motion of such an object by observing the starting times of the transient radio emissions at progressively lower frequencies. The experiment seems simple; unfortunately, however, the above-described phenomenon is quite rare and usually is confused and obscured by other phenomena. Although some tests over a limited range of frequencies have been conducted (*2–4*), the results are inconclusive. However, a clear case of the above-described motion was observed near noon on July 12, 1950. The data of several observers are compiled in Table 1.