sponse of these levels to vitamin D and parathormone administration. However, no clear-cut mechanism for this relation has been suggested.

In the course of a series of investigations[4,5] on the solubility of the basic calcium phosphate system in the region of neutrality, convincing evidence was obtained that normal serum is supersaturated with respect to bone mineral. It was necessary, therefore, to postulate that a cellular mechanism (presumably under the control of the parathyroid glands) exists for maintaining a calcium ion gradient between blood and bone.

It was hypothesized that the cellular elements of bone normally secrete citrate (or citric acid) in response to parathyroid activity. This citrate carries complexed calcium to the serum where extraskeletal tissues (the kidney primarily[3]) oxidize much of the citrate leaving an excess of calcium ion in solution. If citrate were secreted as the acid, a local *p*H gradient would also contribute to the transport of ionized calcium to serum.

It was technically very difficult to test the hypothesis directly. However, by simply drilling a small hole in the spongiosa of the femur of an intact dog it was possible to collect blood directly from the spongiosal circulation for comparison with simultaneous arterial samples. While this sample was only "contaminated" with venous flow from the bone cells, the output of citrate from the bone was so great, clearcut analytical differences were easily shown. Furthermore, dramatic increases in citrate output from the bone were observed almost immediately following injection of parathyroid extract. Simultaneous measurements of the clearance of intravenously administered radiostrontium gave a measure of the proportion of collected sample which was actually venous flow from bone. A typical experiment is summarized in Fig. 1.

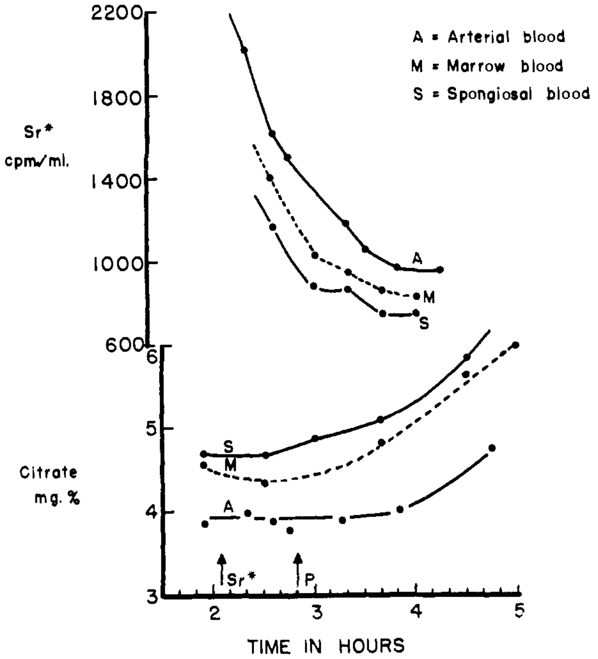

Fig. 1.—Curves showing the citrate production by bone and its response to parathyroid extract injection (arrow P, 1000 units, Eli Lilly Co.). The upper curves show the clearance of carrier-free radiostrontium injected at arrow Sr*). Note that the citrate level is inversely related to the clearance of radiostrontium indicating bone as the source of the citrate. Mixed venous blood from the general circulation, drawn at intervals throughout the experiment, exhibit citrate levels slightly below those of arterial blood.

This direct substantiation of the initial hypothesis was given strong support by enzyme studies *in vitro*. It was found in confirmation of Dixon and Perkins[3] that mature bone lacks isocitric dehydrogenase which is needed for citrate utilization. Furthermore, parathyroid extract was shown spectrophotometrically to destroy the chromophoric group (340 mμ) of reduced Coenzyme II *in vitro* rendering it practically non-absorbent. The nature of this destruction is at present unknown, but consultation of current biochemical texts shows that blocking Coenzyme II-linked reactions shunts all of glucose metabolism ultimately to citrate production. This provides an intriguing biochemical mechanism by which a parathyroid-controlled citrate gradient maintains a steady but supersaturated level of ionized calcium in serum.

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[4] G. J. Levinskas and W. F. Neuman, *J. Phys. Chem.*, **59**, 164 (1955).

[5] B. Strates, W. F. Neuman and G. J. Levinskas, in preparation.

ON THE CONFIGURATION OF CEVINE

Sir:

Evidence is advanced herewith for revision of the configuration at C_{16} in the generally-accepted formulation of cevine.[1,2] The argument also provides a firm basis for assignment of the configuration at C_{20} of cevine which we now propose be represented by formula I.

The susceptibility of the C_{16} acetate esters to base-catalyzed[3] methanolysis—a phenomenon which was regarded as presumptive evidence favoring the α(equatorial)-configuration[1,2]—appeared to us to be abnormally high even for an equatorial ester. This rate of methanolysis, indeed, was found to exceed that of an *unhindered* equatorial ester.[4] In the germine series the C_7 acetate, which is undoubtedly α(axially)-oriented,[5] exhibits comparable reactivity.[6] This behavior prompted us to postulate a facilitation of methanolysis by a hydroxyl group (the α-oriented C_{14} hydroxyl in this

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[1] D. H. R. Barton, O. Jeger, V. Prelog and R. B. Woodward, *Experientia*, **10**, 81 (1954).

[2] D. H. R. Barton, C. J. W. Brooks and P. de Mayo, *J. Chem. Soc.*, 3950 (1954).

[3] W. J. Rosenfelder, *ibid.*, 2638 (1954).

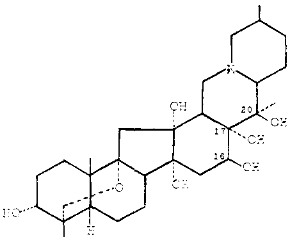
[4] Whereas cevadine-D-orthoacetate 4,16-diacetate (A. Stoll and E. Seebeck, *Helv. Chim. Acta*, **35**, 1942 (1952)) underwent methanolysis in 75% yield after 20 hours in dilute methanol, epiandrosterone 3-acetate was recovered largely (75%) unchanged after similar treatment in the presence of cevine to serve as the base (see ref. 3).

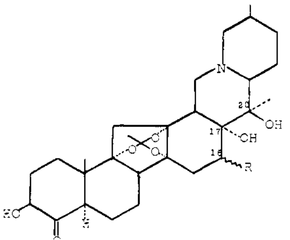
[5] S. M. Kupchan and C. R. Narayanan, *Chemistry and Industry*, in press.

[6] *E.g.*, the facile methanolysis of neogermitrine, J. Fried, P. Numerof and N. M. Coy, THIS JOURNAL, **74**, 3041 (1952).

case) bearing a *cis*-1,3-diaxial relationship to the ester group and thus juxtaposed for participation. This hypothesis was tested by treatment of strophanthidin 3-acetate with dilute methanol and cevine for 20 hours[4]; strophanthidin was isolated in 66% yield.[7]

The C_{16} acetate in the germine series also exhibits this abnormal reactivity.[8] Now this group is evidently β(axially)-oriented[5] which requires, on the basis of a 1,3-diaxial facilitation, a β(axial)-orientation of the C_{20} hydroxyl. It was therefore attractive to postulate similar disposition of the C_{16} and C_{20} hydroxyl groups in cevine. The following experiments establish this point.





II (R = α-OH)
III (R = β-OH)

Hydrogenation of 16-ketocevine 3,4-diacetate[2] over platinum oxide proceeded stereoselectively to give cevine 3,4-diacetate. The molecular model of the ketone shows that the α- is much less hindered than the β-face for approach to the catalyst, suggesting that reaction would proceed to give a β-oriented hydroxyl.

Sodium borohydride reduction of 16-ketocevadine-D-orthoacetate 4-acetate[3] afforded a mixture of cevadine-D-orthoacetate 4-acetate[4] and *16-epicevadine-D-orthoacetate-4-acetate*, m.p. 314–316° dec., $[\alpha]^{21}\text{D} + 65°$ (c, 1.17 chf). (Found: C, 66.21; H, 7.96). The structure of the 16-epi compound was confirmed by oxidation with chromic acid to regenerate the original ketone. In order to liberate the C_{17} hydroxyl group, both epimeric D-orthoacetates were submitted to alkaline hydrolysis followed by treatment with mineral acid to effect rearrangement to the C-orthoacetates.[9] 16 - Epicevagenine - C - orthoacetate (II) crystallized with one molecule of benzene and melted at 276–279° dec., $[\alpha]^{21}\text{D} - 10°$ (c 1.22, chf). (Found: C, 9.09; H, 7.81. The two epimeric C-orthoacetates were compared in their behavior toward lead tetraacetate, and cevagenine-C-orthoacetate[8] was found to react at a strikingly slower rate than the 16-epi compound, suggesting that the hydroxyl groups at C_{16} and C_{17} are *trans*-disposed in the former and *cis*- in the latter. Since the C_{17} hydroxyl group is undoubtedly α-oriented,[2,9] the configurations are established as III and II, respectively.

The established β-configuration of the C_{16} hydroxyl group in cevine now points strongly to a β-configuration for the C_{20} hydroxyl group—a point concerning which there has been considerable doubt.[2,10] We have noted that the C_{16} hydroxyl group of 16-epicevadine-D-orthoacetate 4-acetate is relatively difficult to acetylate. This fact is consistent with the α(equatorial)-configuration for the methyl group at C_{20} which is held rigidly eclipsed with the C_{16} α-hydroxyl group and exerts serious crowding. One is forced to conclude that the simple rules of conformational analysis must be regarded with caution in treating complex structures.[11]

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[7] H. B. Henbest and B. J. Lowell, *Chemistry and Industry*, 278 (1956), have independently presented an elegant demonstration of this effect in the sterol series.

[8] *E.g.*, the facile methanolysis of germine-14,15-acetonide 3,16-diacetate, S. M. Kupchan and C. R. Narayanan, *Chemistry and Industry*, 251 (1955).

[9] S. M. Kupchan, This Journal, **77**, 686 (1955).

[10] F. Gautschi, O. Jeger, V. Prelog and R. B. Woodward, *Helv. Chim. Acta*, **38**, 296 (1955); K. Macek and Z. J. Vejdelek, *Nature*, **176**, 1173 (1955).

[11] This work was supported in part by a grant (H-2275) from the National Heart Institute of the National Institutes of Health.

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BOOK REVIEWS

Conference on Effects of Radiation on Dielectric Materials. NAVAL RESEARCH LABORATORY. OFFICE OF TECHNICAL SERVICES, DEPARTMENT OF COMMERCE, Washington, D. C. (Publication No. PB111863). 1956. v + 169 pp. 20 × 26.5 cm. Price, $4.25.

This is a compilation of reports presented at a conference on the effects of radiation on dielectrics held at the Naval Research Laboratory in December, 1954. It serves primarily as a survey of the scope of development and of interest in the subject at that time in various university, governmental and industrial laboratories. Among the laboratories represented are the University of Notre Dame, Naval Research Laboratory, Carnegie Institute of Technology, Brookhaven National Laboratory, Argonne National Laboratory, North American Aviation Corp., Bausch and Lomb Optical Co., Oak Ridge National Laboratory, Naval Radiological Defense Laboratory, Westinghouse Electric Corp., General Electric Co., National Bureau of Standards, and Knolls Atomic Power Laboratory. The papers include surveys of the radiation chemistry of organic systems and of the radiation synthesis of polymers, three surveys of radiation effects in polymeric systems, four papers on various deleterious aspects of radiation on organic materials, and eleven papers on the radiation physics of the solid state. The solid state papers are concerned with changes in conduction, optical transmission, magnetic susceptibility and lattice parameters in inorganic crystals due both to the effects of γ-rays and to displacements resulting from fast neutron bombardment.

The twenty-one reports vary widely in detail; a one-half page abstract in one case and thirty pages, including eleven of references, in another. A number of the papers appear