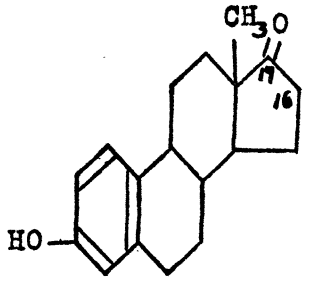
DISCUSSION

THE CHEMICAL TRANSFORMATION OF ESTRONE TO ESTRIOL (THEELOL)

THEELOL was first obtained in 1930 from human pregnancy urine by Marrian[1] and by Doisy.[2] Browne[3] later isolated it from human placenta. Theelol is the principal estrogenic hormone not only in human pregnancy urine but in human placenta as well. Endo-

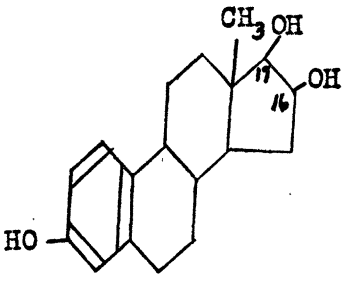


I

crinologists have generally held that theelol (II) arises biologically from the metabolism of estrone (I). That such a conversion can take place is now known with certainty as a result of the recent research of Pearlman and Pincus.[4]

Theelol differs from all other naturally occurring estrogens in possessing a functional group at steroid position 16. Peculiarly, this hormone is found only in the human species. On assay in the intact, immature, female rat it exhibits biological activity[5] much greater than that of its own precursor, estrone. These facts have led to the speculation that the physiological role of theelol may be qualitatively different from that of the other estrogens.

Abnormal estrogen metabolism has long been suspected in the etiology of carcinoma of the genital organs. Three years ago one of us (M.N.H.) commenced work on this problem with the view[6, 7, 8] that such an abnormal metabolism should be sought for generally in the transformation of estrone to theelol and particularly in the formation of an isomeric estriol possessing the unchanged estrone nucleus but



II

differing from theelol in the spatial arrangement of the carbinols at positions 16 and 17. It was in pursuance of this research that the isomeric estriol, isoestriol-A, was prepared.[6, 7] In attempting to make other stereoisomeric estriols of this class the present authors have obtained a small amount of a compound which has proved identical with theelol, the naturally occurring estriol.

We, therefore, wish to report the transformation of estrone to theelol by application of methods of pure organic chemistry. After a seven-step synthesis we obtained a low yield of pure theelol. It crystallized from aqueous methanol in very tiny needles which melted at 268.5–270° (unc.). An authentic sample of theelol kindly supplied by Dr. D. W. MacCorquodale, of the Abbott Laboratories, melted at 268.5–269.5° (unc.). A mixed melting point performed with authentic theelol and our estriol showed no depression. A microanalysis[9] of synthetic estriol gave: C 74.80, 74.76; H 8.46, 8.51 (calculated: C 74.97; H 8.39). There was no depression of the melting point of theelol-3-methyl ether-16,17-diacetate after admixture with the synthetic 3-methyl ether-16,17-diacetate.

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1 G. F. Marrian, *Biochem. Jour.*, 24: 435, 1930.
2 E. A. Doisy, S. A. Thayer, L. Levin and J. M. Curtis, *Proc. Soc. Exp. Biol. and Med.*, 28: 88, 1930.
3 J. S. L. Browne, cited by J. B. Collip, *Proc. Calif. Acad. Med.*, 1: 38, 1931.
4 W. H. Pearlman and G. Pincus, *Jour. Biol. Chem.*, 147: 379, 1943.
5 J. M. Curtis and E. A. Doisy, *Jour. Biol. Chem.*, 91: 647, 1931.
6 M. N. Huffman, *Jour. Am. Chem. Soc.*, 64: 2235, 1942.
7 M. N. Huffman and H. H. Darby, *Jour. Am. Chem. Soc.*, 66: 150, 1944.
8 The reasons for this hypothesis would be out of place in this communication. It is interesting to note that Hirschmann (*Jour. Biol. Chem.*, 150: 363, 1943) has recently isolated from the urine of a patient with adrenocortical carcinoma a Δ^5-androstenetriol-3(β),16,17—a steroid of the androgen series closely comparable to theelol in the estrogen series.

9 Performed by Dr. E. W. D. Huffman, Denver.

ON THE INHIBITION OF UREASE BY PENICILLIN[1]

IN a recent announcement, Turner, Heath and Magasanik[2] reported that urease is inhibited by penicillin preparations. The authors suggested the *in vitro* inhibition of the enzyme as a basis for the assay of penicillin. We have repeated their experiments using urease (Squibb) solutions of 0.1 and 0.5 per

1 Contribution from Research Laboratories, Merck and Company, Inc., Rahway, N. J.
2 J. C. Turner, F. K. Heath and B. Magasanik, *Nature*, 152: 326, 1943.

cent. A low potency preparation containing 1.3 Florey units of penicillin per mg and a sample of crystalline penicillin were used. Typical results are shown in Table 1.

TABLE 1

Urease concentration	Experiment	Mgs NH_3 liberated
0.1 per cent.	Control	0.42
	Crude penicillin (130 units)	0.21
	Crystalline penicillin (1.739 mgs 1650 units per mg)	0.39
0.5 per cent.	Control	2.60
	Crude penicillin (65 units)	0.89
	Crystalline penicillin (1.442 mgs)	2.55

It is clear from the data shown that crude penicillin preparations do, in fact, inhibit urease, but pure samples of the drug do not. It may thus be concluded that the reactions observed by Turner, Heath and Magasanik were produced by the impurities in the comparatively crude preparations of penicillin available to them at the time when they performed their experiments. Since there is no significant inhibition of urease in the presence of as much as 1 to 2 mgs of crystalline penicillin, this approach does not appear to afford a basis for the assay of penicillin.

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ON THE EFFECT OF CONTRAST IN MAKING VISUAL STAR COLOR ESTIMATES

THE writer, at present, is engaged in rechecking visually star colors for all stars visible from latitude 39° N. down to 6th. mag., using low-power, wide-field binoculars and the Yale Catalogue of Bright Stars as reference. The method is to observe a given number of stars, estimating the colors visually; later the list is compared with the Yale Catalogue of spectral classifications and any error in estimates is thus discovered. The writer's color sense, recently tested by the Ishihara method, is a trifle better than normal; and this has been reflected in the accuracy of comparisons, generally running from 80 per cent. to 100 per cent., observing in the heart of the city (Baltimore).

Nevertheless peculiar anomalies occur. On the night of August 19, 1944, at 11h 37 m E.S.T., the color of ψ Capricorni, mag. 4.26, spectral class F_8, was estimated as pale yellow—which was correct. However, the color of ω Capricorni, mag. 4.24, spectral class M_a, also appeared yellow. This star is in the same binocular field with ψ.

Observation of A Capricorni (24 Cap.) mag. 4.6, spectral class M_a, gave a normal, orange-red, Antarean color for this star. Although A Capricorni and ω Capricorni are of the same spectral class, of closely comparable magnitude, and in all visual aspects essentially similar, ω had appeared distinctly yellowish. Reference to an old observation of this star, August 1, 1940, 11 h 35 m E.S.T., showed that at that time the writer had seen the true color without difficulty; but observation then had been with a 2-inch refractor.

Following the suggestion of the earlier observation, ω was re-observed, with a 3-inch refractor. The color now came out quite clearly, the star being like a miniature Antares. It was apparent that the normal color of A Capricorni had been estimated correctly with binoculars because this star stood alone, with no star of comparable magnitude in the same field. When ω was similarly isolated in a telescopic field the true color came out easily. On the other hand, the presence of the yellow star, ψ Capricorni, in the same binocular field with ω, had seriously affected the color estimate of the latter.

This suggests a possible cause, apart from the personal equations, for the widely differing color estimates given for close doubles by the older observers.

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CONSTRUCTIVE MEDICINE

THE recent thought-provoking article by Smith and Evans,[1] attempting to define preventive medicine, reveals how inadequate this term is in modern medical thinking. Though in hearty agreement with the concept of expanding the significance and application of medical practice beyond treatment and prevention of specific diseases, I feel that it might be wiser to apply a new term, rather than to attempt to expand the definition of an old one. As pointed out by Galdston,[2] the term "preventive medicine" will always be limited by the meaning of the word "prevention."

Preventive medicine was a vast step forward in the days when health was defined as that state of being existing in the absence of disease. But medicine has outgrown this older definition of health. Health is more than the absence of demonstrable disease. Health is always relative. It is no more absolute than freedom, slavery, beauty, poverty or wealth. Yet these terms, and many others with similar abstract connotations, are used habitually so loosely that implication of absolute values has crept into our thinking. Health has quantitative attributes involving functional reserve capacities. There are degrees of health. Perfection can be only an ideal abstraction. Perfect health is probably unattainable, though it may be approached. Optimum health implies a maximum reserve capacity for every organ and function of the organism.

[1] G. Smith and L. G. Evans, SCIENCE, 100: 39, July 21, 1944.
[2] I. Galdston, SCIENCE, 100: 76, July 28, 1944.