tion of the reversal of the vasomotor effect, will be described separately.

We thank Prof. F. Bergmann for his advice.

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[1] Butterworth, K. R., *Nature*, **198**, 897 (1963).
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It is interesting to see in the preceding communication that Gutman and Beyth have obtained, using isoprenaline or adrenaline as reversing agents in the spinal cat, similar results to Walz, Koppanyi and Maengwyn-Davies[1]. However, several points seem to require clarification. As I have said previously[2a], I do not consider that the effects obtained by these workers are produced by the same mechanism as are obtained when larger doses of isoprenaline are given. I have suggested[2b] that, when larger doses are given, the first dose produces β-adrenergic blockage and this then reveals the weak α-adrenergic activity of isoprenaline, thus causing a rise in blood pressure. It is probable that when smaller doses of isoprenaline are given they are insufficient to produce a β-blockade.

I agree that after administering a β-adrenergic blocking drug one would expect to see a potentiation of adrenaline, and this I found[2c]. Frequently, as might be expected, there was a loss in sensitivity to adrenaline until the blood pressure had returned to its pre-blocking level. This might afford a simple explanation of the results of Gutman and Beyth shown in their Fig. 3*b*, where the blood pressure is half that of Fig. 3*a*. The potentiation that they observed after nethalide (pronethalol) could be explained by the increased resting blood pressure. To guard against losses of sensitivity due, for example, to the poorer condition of the animal when the blood pressure is lowered, I used noradrenaline as an indicator of sensitivity. An argument for the isoprenaline causing β-blockade is the alteration in the ratio of equi-pressor doses of adrenaline to noradrenaline following the administration of large doses of isoprenaline, from a value of about three to a value nearer to one. This I found[2c]. The experiments of Gutman and Beyth were not designed to reveal any such changes.

Since isoprenaline may be regarded as the parent of a series of β-blocking drugs, including the well-known substances nethalide and dichloroisoprenaline, is it not reasonable that isoprenaline should have β-adrenergic blocking activity? As such, I have found that it is at least as active as these two substances.

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[1] Walz, D. T., Koppanyi, T., and Maengwyn-Davies, G. D., *J. Pharmacol. and Exp. Therap.*, **129**, 200 (1960).
[2] Butterworth, K. R., *Brit. J. Pharmacol.*, **21**, 378 (1963). (*a*) 390; (*b*) 388; (*c*) 382, Fig. 2, 385, Fig. 5, 391.

PATHOLOGY

Production of Unconjugated Hyperbilirubinæmia in Full-term New-born Infants following Administration of Pregnane-3(alpha), 20(beta)-diol

We have previously described a syndrome of severe and prolonged unconjugated hyperbilirubinæmia associated with breast feeding in seven full-term new-born infants in whom no other cause of jaundice was found[1]. The highest serum bilirubin concentrations in these infants were 14·3–24·5 mg per cent and were observed between the 10th and 19th days of life. Following abrupt cessation of breast feeding, hyperbilirubinæmia disappeared in 2–6 days. Milk from the mothers of these jaundiced infants consistently inhibited hepatic glucuronyl transferase activity *in vitro*, while milk from mothers whose children were normal did not. 150–400 c.c. of milk from three of the mothers was examined in an attempt to identify an inhibitor. In each of the three cases investigated a steroid was isolated and identified as pregnane-3(α), 20(β)-diol. This steroid competitively inhibits glucuronyl transferase activity *in vitro*. From the quantity of pregnane-3(α), 20(β)-diol isolated from milk, we estimated that the jaundiced infants ingested approximately 1·0 mg of steroid per day.

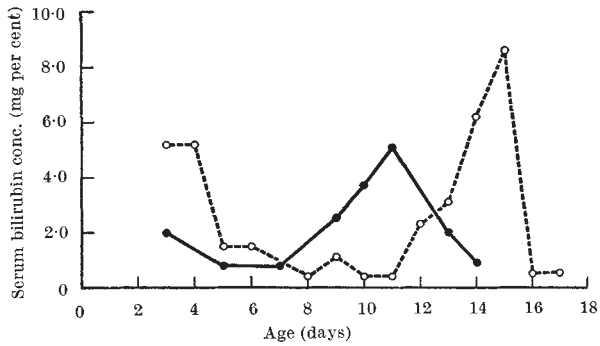

Fig. 1. Effect of ingestion of pregnane-3 (*α*), 20 (*β*)-diol on the serum bilirubin concentration in two full-term new-born infants. 1 mg/day P.O.; —, baby *A*; – – –, baby *B*

Numerous attempts were made to demonstrate an effect of pregnane-3(α), 20(β)-diol on the hepatic metabolism of bilirubin in Wistar and Gunn rats and guinea pigs *in vivo*. The results were inconclusive, possibly due to differences in absorption, distribution and metabolism of the steroid in these species as compared with man. An attempt was then made to produce the syndrome artificially in full-term new-born infants.

The following considerations supported the safety of administering pregnane 3(α), 20(β)-diol to full-term new-born infants in the amounts isolated from inhibitory milk. None of the breast-fed infants of mothers whose milk contains the steroid demonstrated signs or symptoms of kernicterus. In addition, cessation of breast feeding by these infants was associated with rapid return of serum bilirubin concentrations to normal, making it probable that any rise in the serum bilirubin concentration could be promptly and safely reversed.

Pregnane-3(α),20(β)-diol was suspended in liquid vitamin drops and administered orally (0·33 mg/kg body-wt./day) in divided doses every 4–6 h to four healthy, full-term infants starting at 6, 8, 34 and 66 days of age, respectively, and to one adult male. The infants were selected at random and there was no previous history of jaundice associated with breast feeding in their siblings.

Hyperbilirubinæmia was not observed in the two older infants who received the steroid for 12 days nor in the adult who ingested the steroid for 10 days. The results in the two youngest infants are presented in Fig. 1. In baby *A*, physiological jaundice remitted by day 5 and on day 6 steroid administration was begun. Five days later the serum bilirubin concentration was 5·1 mg per cent; steroid administration was discontinued and the serum bilirubin concentration became normal in 3 days. In baby *B*, physiological jaundice disappeared by day 8 and steroid administration was begun. The serum bilirubin concentration remained normal until four days later when it was 2·3 mg per cent. Three days later the serum bilirubin concentration was 8·6 mg per cent and steroid administration was discontinued. The serum bilirubin concentration became normal 24 h later. In none of