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

We thank Prof. F. Bergmann for his advice.

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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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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.

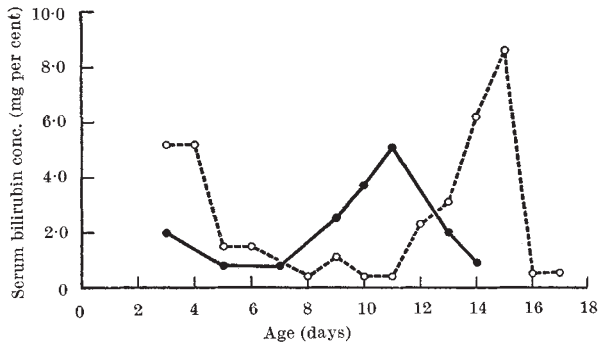

Fig. 1. Effect of ingestion of pregnane-3 (*α*), 20 (*β*)-diol on the serum bilirubin concentration in two full-term new-born infants. 1 mg/day P.O.; —, baby *A*; – – –, baby *B*

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

these determinations did the serum direct-reacting bilirubin concentration exceed 25 per cent of the total serum bilirubin concentration and usually was less than 10 per cent of the total bilirubin. Hæmoglobin concentrations, reticulocyte counts and serum glutamic–pyruvic and glutamic–oxaloacetic transaminase activities, thymol turbidity, cephalin cholesterol flocculation and the concentration of albumin and globulin remained normal throughout the investigation of each of the five subjects.

This work demonstrates that unconjugated hyperbilirubinæmia can be produced in very young, full-term infants by feeding pregnane-3(α), 20(β)-diol in amounts equivalent to that isolated from inhibitory human milk. Only very young infants became jaundiced after ingestion of pregnane-3(α), 20(β)-diol because the exogenous inhibitor is probably superimposed on the already limited hepatic conjugating capacity of the new-born[2–4]. There appears to be nothing unique about the infants of the mothers whose milk contains the inhibitor.

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Origin of Plasma Cells in Sites of Inflammation

The origin of plasma cells in inflammatory reactions in non-lymphoid tissue is perplexing. They are found in the circulation only in unusual circumstances[1] and are not a usual cellular component of normal connective tissue. A possible source of these cells in areas of injury is suggested from investigations of lymphocytic cells in the vascular spaces and alveolar walls of the lung following the intravenous injection of complete Freund's adjuvant. The changes in some of these lymphocytes are similar to those described for white cells of the peripheral blood grown in tissue culture in the presence of a variety of materials. When phytohæmagglutinin, tuberculin, tetanus toxoid, diphtheria toxoid, smallpox vaccine, hæmophilus pertussis antigen, staphylococcal antigen, leukocyte antiserum, pollen extract and various tissue antigens are added to cultures of white cells from the peripheral blood, the small and medium sized lymphocytes enlarge and mitotic division may occur[2–13]. Tanaka *et al.*[14] have described a developing Golgi apparatus, increased ribosomes and a small amount of endoplasmic reticulum in cultures of lymphocytes from peripheral blood.

In addition to these changes, Bach and Hirschhorn[15] demonstrated that some of the lymphocytes grown in culture in the presence of tuberculin contain gamma globulin and in the presence of phytohæmagglutinin contain 7*S*γ 2 globulin. A few of the lymphocytes in their cultures eventually had the appearance of 'plasma-like cells'.

Albino rabbits, which had been given 1 ml. of complete Freund's adjuvant intravenously, were killed at 15 min, 30 min, 1 h, 12 h and 1 and 3 days after injection. Four rabbits which had not received adjuvant were used as controls. Samples of lung were fixed and embedded for electron microscopy.

Examination of the lungs from normal rabbits showed an occasional lymphocyte in the vascular spaces and none in the extravascular tissue of the alveolar walls. These cells had the ultrastructural features of lymphocytes obtained from the peripheral blood as described by Low and Freeman[16].

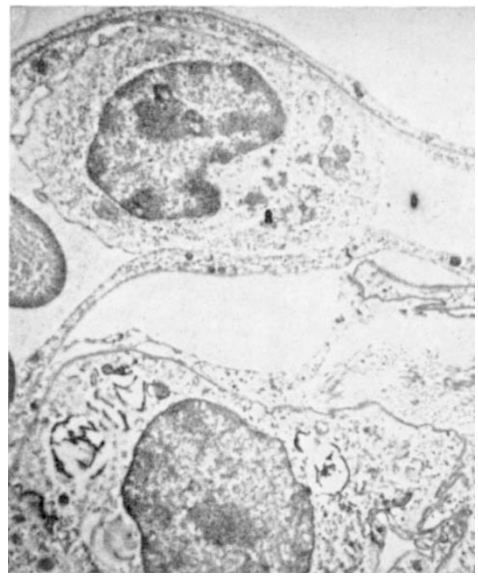

Fig. 1. Lymphocytic cell in the capillary of an alveolar wall from a rabbit killed 15 min after receiving Freund's adjuvant

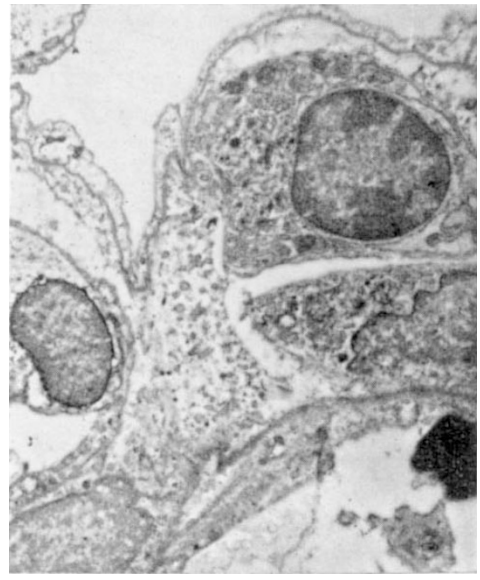

Fig. 2. 'Plasma-like cell' in the alveolar wall from a rabbit killed 30 min after the injection of adjuvant

Fifteen min after the intravenous injection of the adjuvant the number of white blood cells in the vascular spaces of the lungs was markedly increased, and a few of the cells had migrated across the vascular walls into the alveolar septa. Some of the small and medium sized lymphocytic cells, while still in the vascular spaces, showed an increase in ribosomes and a small amount of endoplasmic reticulum and a more prominent Golgi apparatus (Fig. 1). These ultrastructural changes continued after the migration of the cells into and across the walls of the vascular channels (Fig. 2). By 1–3 days after the injection many of the intraluminal lymphocytic cells had acquired a cytoplasmic ultrastructure similar to plasma cells. It is apparent that 'plasma-like cells' can develop from small and medium lymphocytes.