The high absorption in lupoid hepatitis is interesting in that R. Williams (personal communication, 1965) has also found a high iron absorption in this condition; that this is not due to accompanying pancreatic damage is suggested by the finding that neither of these two patients showed a diminished iron absorption when the test was repeated with the addition of pancreatin. A third patient with infectious hepatitis also showed no change in absorption with the addition of pancreatin.

The condition produced in rats by α -naphthyl isothiocyanate has been described as "experimental cirrhosis." It is a chemical damage characterized by massive proliferation of biliary epithelial cells, which occurs not only to areas recovering from coagulative necrosis of the parenchyma but also independently (Steiner and Carruthers, 1963). It is debatable, of course, whether this can be regarded as comparable to hepatitis of man. Nevertheless, the liver changes which were produced in our test animals did not influence iron absorption. Higginson *et al.* (1963) also showed no effect on iron absorption in rats in which chronic liver damage had been produced by carbon tetrachloride.

Summary

Absorption of iron-59 in the form of ferrous sulphate and labelled haemoglobin has been tested in patients having various forms of acute hepatitis. Iron absorption was in the lower range of normal in patients with acute liver disease, except those who had lupoid hepatitis or iron deficiency. Pancreatic extract did not affect the absorption of iron in these patients. Chemical liver damage in rats did not affect iron absorption.

REFERENCES

- Bothwell, T. H., and Mallett, B. J. (1955). *Biochem. J.*, **59**, 599.
 Callender, S. T., Mallett, B. J., and Smith, M. D. (1957). *Brit. J. Haemat.*, **3**, 186.
 Callender, S. T., and Malpas, J. S. (1963). *Brit. med. J.*, **2**, 1516.
 Higginson, J., Grady, H., and Huntley, C. (1963). *Lab. Invest.*, **12**, 1260.
 McCall, M. G., Newman, G. F., O'Brien, J. R. P., Valberg, L. S., and Witts, L. J. (1962). *Brit. J. Nutr.*, **16**, 297.
 Peterson, R. E. (1952). *J. Lab. clin. Med.*, **39**, 225.
 Steiner, J. W., and Carruthers, J. S. (1963). *Lab. Invest.*, **12**, 471.
 Turnberg, L. A. (1966). *Amer. J. dig. Dis.*, **11**, 20.
 Van de Kamer, J. H., Huinink, H. ten B., and Weyers, H. A. (1949). *J. biol. Chem.*, **177**, 347.

Increased Factor IX Levels in Puerperium during Administration of Diethylstilboestrol

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The administration of diethylstilboestrol for the suppression of lactation has been reported to increase the incidence of puerperal thromboembolism (Daniel *et al.*, 1967). Though a relation between increased levels of coagulation factors in blood and thromboembolic disease has not been firmly established in vivo, there is evidence that the activity of factors IX, XI, and XII is essential for the development of thrombus in the ligated veins of experimental animals (Wessler and Reimer, 1960).

The present paper describes the results of a study of factor IX levels in the plasma of puerperal women and reports the new observation that diethylstilboestrol administration causes a highly significant increase in factor IX level.

Method

All patients investigated had a normal labour and puerperium. There were no thromboembolic episodes. One group was lactating; in the second group lactation was suppressed without the use of oestrogens, diuretics, or changes in fluid intake—"natural suppression"; and in the third group lactation was suppressed by the administration of diethylstilboestrol (10 mg. t.i.d. for three days; 10 mg. b.d. for three days; and 10 mg. daily for three days)—"stilboestrol suppression." Treatment was begun on the first day of the puerperium, the first dose of diethylstilboestrol being given at 6 a.m. each day.

At 8 a.m. 4.5 ml. of venous blood was obtained without stasis and added to 0.5 ml. of 3.8% sodium citrate. Factor IX was assayed "blind"—that is, without knowledge of the group to which the patient belonged. The technique used was a standard one-stage method similar to that described by Hardisty and Ingram (1964), utilizing a kaolin-activated system consisting of stored (-20° C.) plasma from a patient with severe factor IX deficiency, adsorbed fresh normal plasma to supply factors VIII and V, and phospholipid. The mean value in non-pregnant adults was 100%, with a normal range of 50 to 150%.

Results

Altogether 171 estimations were performed in 111 mothers—64 in the 43 lactating patients, 79 in the 48 who had "stilboestrol suppression," and 28 in the 20 who had "natural suppression." The mothers who had duplicated assays did not differ significantly from those with a single assay, and it is proposed to analyse all the estimations irrespective of whether or not they were duplicates. The obstetric characteristics of these women were recorded and their mean age, parity, duration of labour, and estimated blood loss are shown in Table I.

TABLE I.—Mean Age, Parity, and Duration of Labour and Blood Loss of All Patients

Characteristic	Lactating Group	Stilboestrol Group	Natural Suppression
Mean age (years)	27.1	25.1	27.0
Mean parity	1.0	1.3	1.6
Mean duration of labour (hours)	9.2	7.0	4.5
Mean estimated blood loss at delivery (ml.)	128	123	150

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for each of the three lactation groups. There is no statistical difference in these means between the groups of mothers.

The Chart shows the mean levels and the standard error of the mean of factor IX as percentages (100% being the normal mean) analysed for each day after delivery, within each lactation group. The days were calculated to the nearest whole hour after delivery.

Mean factor IX levels, with standard error of the means, in late pregnancy and in the puerperium (all parties). ---- Stilboestrol. — Lactating. Natural suppression.

Eight estimations performed in pregnant patients at full term had a mean value of 132%, with a standard error of ± 17.8 . This result is not distinguishable statistically from the mean level in the puerperium in lactating or naturally suppressed women.

On every day after delivery the mean level in the stilboestrol group was higher than that in the lactating group to such an extent that in the Chart the standard errors of the means do not overlap.

The 28 assays on the 20 mothers who had natural suppression of lactation are not statistically different from those of the lactating group with a mean of 143% and a standard error of ± 9.1 %.

Analysis of variance shows that the difference between the lactating and stilboestrol groups of mothers is statistically significant, with the possibility of the two series of results arising from a single homogenous group being less than 1 in 1,000. The variances within both these groups (lactating and stilboestrol) are very similar; the mothers in the stilboestrol group were just as variable between themselves as were the lactating mothers but around a higher mean.

Parity has a very marked effect on factor IX levels in the stilboestrol group. Table II shows that the lower the parity the more pronounced the difference between the stilboestrol and the lactating groups. The incidence of assays of 200% or more demonstrates this point. In parity 0 patients 58% of assays are over 200% in the stilboestrol group but only 5% in the lactating group. In parities 1 and 2 the comparable

figures are 38 and 6%, and in the higher parities two out of eight (25%) assays are above 200% in the stilboestrol group but none in nine lactating patients. Moreover, the proportion of the stilboestrol group in which the factor IX assays were *more than double* the mean for the comparable lactating group was 25% in para 0, 11% in para 1 and 2, and none in para 3 and over.

Age has no demonstrable effect on the factor IX level.

The analysis of variance suggests that there is no trend in the factor IX level during the first nine days after delivery other than an increase which occurs on the third day (see Chart). This peak is seen in both the lactating group and the stilboestrol group.

Discussion

Investigation of factor IX levels in pregnancy has given results varying from no change (Nilsson and Kullander, 1967a) to slight elevation within the normal range (Ross, 1963; Kasper *et al.*, 1964; Todd *et al.*, 1965) and to a marked elevation (Ratnoff and Holland, 1959). In labour, factor IX has been found to be raised slightly (Fresh *et al.*, 1956), and this increase persists for at least 20 minutes after delivery (Nossel *et al.*, 1966). Nilsson and Kullander (1967a) found no increase during the first four days of the puerperium, but Davidson and Tomlin (1963) found the mean level of readings taken between the seventh and the tenth day of the puerperium to be nearly twice their control mean. However, neither parity nor method of feeding was indicated in these puerperal studies. We have found no references to the effect of oestrogens on factor IX levels, and reports on the effect of oral contraceptives are at variance (Rutherford *et al.*, 1964; Nilsson and Kullander, 1967b).

Our results show that mean factor IX levels are above the normal mean in late pregnancy and that in the puerperium patients who are lactating or undergoing natural suppression show little change in the level except a possible increase on the third day.

In puerperal patients receiving diethylstilboestrol a higher level of factor IX is established by the third day, and this is sustained for the first nine days of the puerperium at a mean level well above the range accepted as normal. This is most pronounced in women of low parity but still present in the higher parities.

Of all the coagulation factors, factor IX, together with factors XI and XII, probably plays a major part in the pathogenesis of venous thrombosis. Wessler and Reimer (1960) showed that, in the rabbit, ligation of a vein did not produce a thrombus, but if human serum was given to the animal less than two minutes before ligation a solid thrombus formed. Serum deficient in factors V, VII, VIII, and X still produced a thrombus, but serum deficient in factors IX, XI, and XII did not. While there is at present no evidence that raised levels of clotting factors accentuate thrombus formation in man, factor IX clearly plays a critical part in serum-induced venous thrombosis in animals. Though the use of kaolin in our assay system on plasma makes it uncertain that the factor IX measured by us is the same as the coagulant activity responsible for the thrombotic effect of serum demonstrated by Wessler *et al.* (1967), it is tempting to postulate that the very high levels of factor IX observed in the present study may be related to the development of puerperal venous thrombosis. It seems particularly significant that the most marked effect of diethylstilboestrol in elevating factor IX levels has been found in women of low parity, as it is in such women that the drug has the greatest effect in increasing the incidence of puerperal thromboembolism (Daniel *et al.*, 1967). Unfortunately we have no data on the effect of diethylstilboestrol on factors XI and XII.

The liver plays an important part in the production and inactivation of factor IX. It also modifies the production of

TABLE II.—Percentage Level of Factor IX Showing Parity and Lactation Group. Number of Readings in Parentheses

Parity	Lactation Group	Day After Delivery				All Days	S.E. of Mean
		Day 2	Day 3	Day 4	Days 5-9		
Para 0	Lactating	(3) 112	(10) 162	(5) 127	(19) 116	(37) 132	± 9.9
	Stilboestrol	(3) 213	(3) 253	(3) 197	(15) 214	(24) 217	± 12.6
Para 1 and 2	Lactating	(4) 102	(2) 155	(4) 126	(8) 139	(18) 130	± 11.2
	Stilboestrol	(10) 141	(11) 211	(3) 165	(23) 172	(47) 174	± 8.4
Para 3	Lactating	(2) 155	(2) 145	(3) 157	(2) 125	(9) 147	± 12.4
	Stilboestrol	(2) 170	(2) 147	(1) 190	(3) 177	(8) 172	± 12.2
All parities	Lactating	(9) 117	(14) 159	(12) 134	(29) 123	(64) 132	± 6.6
	Stilboestrol	(15) 159	(16) 211	(7) 182	(41) 188	(79) 187	± 6.8

serum-induced thrombosis, for if the serum is injected into the portal vein thrombotic activity is much more transient, while ligating the portal vein prolongs thrombotic activity (Wessler *et al.*, 1967). Tindall (1966) has shown that oral contraceptives reduce the rate of elimination of bromsulphalein into the bile while apparently increasing hepatic blood flow, and diethylstilboestrol alone is now known to have a similar effect (Clinch and Tindall, 1968). The increased levels of factor IX in puerperal women receiving diethylstilboestrol may be due to the effect of this drug on liver function.

The effect of the administration of diethylstilboestrol on this single coagulation factor is reported for three reasons. First, though we are investigating changes in fibrinogen and other coagulation factors in these patients, the changes in factor IX levels are already statistically significant at 0.001 level. Secondly, factor IX is of interest in relation to thromboembolism, and our findings may be of relevance in view of the increased incidence of this disease in women receiving oral contraceptives (Medical Research Council, 1967), in puerperal women receiving diethylstilboestrol (Daniel *et al.*, 1967), and in men treated with oestrogens for coronary thrombosis (Oliver and Boyd, 1961). Finally, the findings also suggest a possible new approach to the management of factor IX deficiency (Christmas disease).

Summary

Factor IX levels in plasma have been estimated in late pregnancy and in the puerperium. Puerperal administration of diethylstilboestrol was accompanied by significantly higher factor IX levels than were found in late pregnancy or in the puerperium in women who were lactating or in whom lactation had been suppressed without the use of drugs. This difference

was most pronounced in women of low parities. The finding is discussed in relation to the observation that factors IX, XI, and XII influence venous thrombosis *in vivo*, and also in relation to the reported association between oestrogen administration and thromboembolism.

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REFERENCES

- Clinch, J. A. D., and Tindall, V. R. (1968). *Proc. Brit. pharmacol. Soc.* In press.
 Daniel, D. G., Campbell, H., and Turnbull, A. C. (1967). *Lancet*, **2**, 287.
 Davidson, E., and Tomlin, S. (1963). *J. clin. Path.*, **16**, 112.
 Fresh, J. W., Ferguson, J. H., and Lewis, J. H. (1956). *Obstet. and Gynec.*, **7**, 117.
 Hardisty, R. M., and Ingram, G. I. C. (1964). *Bleeding Disorders: Investigation and Management*. Oxford.
 Kasper, C. K., Hoag, M. S., Aggeler, P. M., and Stone, S. (1964). *Obstet. and Gynec.*, **24**, 242.
 Medical Research Council (1967). *Brit. med. J.*, **2**, 355.
 Nilsson, I. M., and Kullander, S. (1967a). *Acta obstet. gynec. scand.*, **46**, 273.
 Nilsson, I. M., and Kullander, S. (1967b). *Acta obstet. gynec. scand.*, **46**, 286.
 Nossel, H. L., Lanzkowsky, P., Levy, S., Mibashan, R. S., and Hansen, J. D. L. (1966). *Thrombos. Diathes. haemorrh. (Stuttg.)*, **16**, 185.
 Oliver, M. F., and Boyd, G. S. (1961). *Lancet*, **2**, 499.
 Ratnoff, O. D., and Holland, T. R. (1959). *Ann. N.Y. Acad. Sci.*, **75**, 626.
 Ross, R. A. (1963). *Amer. J. Obstet. Gynec.*, **86**, 77.
 Rutherford, R. N., Hougie, C., Banks, A. L., and Coburn, W. A. (1964). *Obstet. and Gynec.*, **24**, 886.
 Tindall, V. R. (1966). Blair Bell Lecture, Royal College of Obstetricians and Gynaecologists.
 Todd, M. E., Thompson, J. H., Bowie, E. J. W., and Owen, C. A. (1965). *Mayo Clin. Proc.*, **40**, 370.
 Wessler, S., and Reimer, S. M. (1960). *J. clin. Invest.*, **39**, 262.
 Wessler, S., Yin, E. T., Gaston, L. W., and Nicol, I. (1967). *Thrombos. Diathes. haemorrh. (Stuttg.)*, **18**, 12.

Presentation of Midgut Malrotation in Adults

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Though midgut malrotation is a common cause of intestinal obstruction in the newborn, scant attention is given to this developmental anomaly as a cause of symptoms in adults. The standard textbooks describe the features of this neonatal obstruction, and then mention that the condition may first present as a great rarity in later life.

In the past 18 months five adults with recurrent symptoms due to midgut malrotation have presented to one surgical firm in St. Thomas's Hospital. These cases have had many features in common, so much so that when the fifth patient attended the outpatient department the correct diagnosis was made on the history and clinical features alone.

Each patient gave a story of recurrent attacks of abdominal colic since childhood. These were often severe and lasted up to 72 hours; then the pain settled spontaneously. In two cases the end of the attack was sometimes accompanied by a bout of blood-stained diarrhoea. Each case had been variously diagnosed and treated previously; in two of them barium studies of the stomach and duodenum only had failed to reveal the true condition.

These cases are described below, and the clinical features and radiographic and operative findings are discussed.

Case 1

A man aged 20 was admitted to hospital as an emergency case in February 1966. He gave a history of severe abdominal colic and vomiting for 72 hours. He had had similar attacks of central abdominal colic frequently since early childhood. Each attack would last about 48 hours and then settle spontaneously. No satisfactory diagnosis had been made, and on one occasion he had been disciplined for malingering when an attack coincided with the end of a period of leave from the Services. A previous barium-meal examination was reported as showing "a normal stomach and duodenum."

On admission to St. Thomas's he had generalized abdominal tenderness, an empty rectum, and all the signs of dehydration due to his vomiting. An emergency laparotomy showed a midgut volvulus, and at its apex a persistent vitello-intestinal duct connected the mass of intestines to the umbilicus. An enteric cyst and a urachal remnant were also present at the umbilicus. After these abnormal ducts and cysts had been divided from the small gut a complete midgut malrotation was found, with the small intestine lying in the right abdomen. The midgut arose from a single long

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