TABLE II.—Effect of C6 on Blood Pressure
(100 mg. C6 Intramuscularly)

Case No.	Supine		Case No.	Standing for 10 min. periods	
	Resting B.P. (Before C6)	Lowest B.P. Observed after C6		Resting B.P. (Before C6)	Lowest B.P. Observed after C6
1	100/75	95/65	7	100/70	95/65*
2	120/90	110/80	8	110/80	100/70
3	110/80	100/75	9	120/80	110/75
4	110/70	110/70	10	110/70	90/70*
5	110/85	110/85	11	110/80	100/80
6	95/60	95/60	12	115/85	95/65

* Faintness relieved by lying down.

pressure (Table II) and a slight increase in pulse rate. Throughout the investigations the patients were allowed up on several occasions and felt no subjective effects except in two instances.

In these two cases there was a transitory feeling of faintness, quickly relieved on lying down.

Subjective.—There were no untoward subjective effects

in this series. Those patients who at the time of injection had ulcer pain were quickly relieved, and all patients remained free from pain for at least five hours. Hunger sensation was diminished in all cases for three to four hours. This was not accompanied by nausea. Accommodation was slightly impaired in one case in this series. (In more recent cases this side-effect has been more frequent.) Curare-like effects such as ptosis and muscular weakness did not occur. During the period of investigation, which involved several injections of hexamethonium iodide, only one patient complained of constipation. This may have been due to the changes incidental to hospital routine and not to repeated administration of the drug.

Discussion

Our observations show that hexamethonium iodide, when given intramuscularly, inhibits the spontaneous secretion of hydrochloric acid. A single dose of 100 mg. produces achlorhydria for as long as three hours. Repeated doses effect a substantial reduction in the volume and acidity of the night secretion.

The fact that this compound prevents the development of a true insulin response suggests that it acts by vagal blockade. This is in keeping with its known pharmacological action as observed in the experimental animal (Paton and Zaimis, 1949). That it fails to prevent a histamine response is in keeping with the view that histamine acts directly on the parietal cell.

Our observations show also that hexamethonium iodide has a pronounced inhibitory effect on the movements of the stomach. One of us has had the opportunity of testing the effect on gastric motility of many antispasmodic drugs. The four-hour period of inhibition after hexamethonium iodide is greater than has been observed after any other agent. The cessation of gastric contractions and tonus waves is as complete as that resulting from vagal section.

Hexamethonium iodide appears to have several advantages over other drugs with a similar pharmacological action. It is more uniform in its effect, more potent, and of longer duration, and it is relatively free from untoward side-effects.

It seems likely that hexamethonium iodide may have a value in the treatment of peptic ulcer. Certainly it is the most effective drug yet available as an inhibitor of gastric secretion and motility. Up to the present we have employed repeated injections of uniform dosage, and this method is practicable for in-patient treatment. Further observations are in progress on the effects of larger doses, on the use of media for retarding absorption, and on the possibility of oral administration.

Summary

In 10 patients with active duodenal ulcer, hexamethonium iodide inhibited the spontaneous secretion of hydrochloric acid to the point of achlorhydria.

It modified the secretory response to insulin-induced hypoglycaemia but did not affect the response to histamine.

It reduced the volume and acidity of the 12-hour spontaneous night secretion.

It produced prolonged inhibition of gastric motor activity.

The high potency of hexamethonium iodide and

its comparative freedom from undesirable side-effects suggest its use in the treatment of peptic ulcer.

We are indebted to Professor C. F. W. Illingworth for his direction and helpful criticism throughout this investigation and to Dr. F. S. Preston and Dr. J. B. Ritchie for recording observations on blood pressure. Our thanks are also due to May and Baker Ltd. for specially preparing the supplies of hexamethonium iodide.

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CHANGES IN SIZE OF RED CELLS DURING NORMAL PREGNANCY

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Wintrobe and Shumacker (1935) have shown that foetal haemopoiesis is similar to that of patients recovering from pernicious anaemia. Assays of livers of pig foetuses for anti-anaemic potency failed to demonstrate activity save in slight degree in the last third of the gestation period (Wintrobe *et al.*, 1937). If anti-anaemic substance is required for blood formation in the foetus it must be supplied by the mother, so that foetal needs represent an added burden to the pregnant woman. Moreover, Miller and Studdert (1942) noted the common occurrence of defective diets in women suffering from pernicious anaemia of pregnancy. It seems possible that women called on to provide

FIG. 7.—Effect of C6 on gastric motility.

extra anti-anaemic factor during normal pregnancy might show relative deficiency insufficient to cause clinically detectable anaemia but producing measurable changes in the size or other features of the erythrocytes. It is the purpose of this paper to report the results of an investigation of this problem.

Material and Methods

Sixteen healthy pregnant women were examined at monthly intervals from the time they were first seen at the antenatal clinic. They rested in the recumbent position for 30 minutes before the collection of blood. Haemoglobin was estimated by the alkaline haematin method (Clegg and King, 1942).

Red and white cell counts were carried out on heparinized venous blood within half an hour of collection. The mean corpuscular volume (M.C.V.) was calculated from the cell volume obtained by centrifugation at 3,000 r.p.m. until a constant volume was reached. The mean corpuscular diameter (M.C.D.) was measured by the method of Price-Jones (1933), dry films stained with Leishman's stain being used.

Results

The results of haemoglobin estimations and red cell counts are shown in Table I.

TABLE I.—Haemoglobin and Red Cell Levels in Normal Pregnancy. (Haemoglobin in Grammes per 100 ml. Blood. Red Cells in Millions per c.mm. Blood)

Case No.	Value	Month of Pregnancy							
		2	3	4	5	6	7	8	9
1	Haemoglobin			13.8	13.8	14.2	12.8	13.0	12.8
	Red cells			4.16	4.26	4.53	4.20	4.63	4.63
2	Haemoglobin	13.6	13.1	12.6	12.5	11.9	11.2	12.3	11.0
	Red cells	4.66	4.11	4.25	3.92	3.85	3.55	3.45	4.20
3	Haemoglobin					14.4	12.5	12.5	12.7
	Red cells					4.69	4.23	4.76	4.39
4	Haemoglobin			13.6	13.2	13.4	12.9	13.5	
	Red cells			4.00	4.44	4.10	3.72	4.09	
5	Haemoglobin			12.8	10.6	12.1	13.4	10.8	
	Red cells			4.36	4.00	3.63	4.04		
6	Haemoglobin		12.4	11.9	12.6	11.9	12.6		
	Red cells		4.26	4.00	3.99	3.72	4.32		
7	Haemoglobin		13.8	12.5	12.7	11.9	11.4	11.0	
	Red cells		4.88	4.87	4.33	4.05	3.87	3.93	
8	Haemoglobin	13.2	12.3	13.6	13.3	12.0	11.9	11.2	10.7
	Red cells	4.63	4.44	4.52	4.58	3.92	4.24	3.90	4.44
9	Haemoglobin	13.5	12.7	14.3	13.8	13.6	13.2	12.7	12.9
	Red cells	4.34	3.99	4.57	5.08	4.56	4.73	4.51	4.24
10	Haemoglobin			13.6	14.0	14.0	14.0	13.6	14.0
	Red cells			4.31	5.02	4.42	4.07	4.43	4.00
11	Haemoglobin		13.2	12.0	11.6		11.8	11.8	11.9
	Red cells		5.43	3.83	3.63		3.57	4.21	4.43
12	Haemoglobin			13.6	12.7	11.2	10.7	9.6	10.5
	Red cells			5.15	5.11	3.71	3.73	4.12	4.18
13	Haemoglobin			13.2	13.6	13.3	12.1	11.6	11.6
	Red cells			4.37	4.99	4.24	3.70	3.95	3.88
14	Haemoglobin			12.0	13.2		12.3		13.7
	Red cells			4.55	4.41		3.76		4.01
15	Haemoglobin		13.3	14.2	15.3	15.3	15.1	13.8	
	Red cells		4.61	6.13	5.57	5.45	5.38		4.74
16	Haemoglobin		12.8	13.4	12.9	12.2	14.2	14.8	
	Red cells		3.73	4.06	3.96	3.83	3.91	4.23	

The lack of agreement on what are the normal haematological standards in pregnancy is due mainly to the wide variation from subject to subject of the physiological hydraemia of pregnancy. In spite of the very many observations of haemoglobin and of the red cell count in pregnancy (Strauss and Castle, 1932; Boycott, 1936) there is no very extensive agreement on what are the normal ranges for these two observations. For haemoglobin levels it has been suggested that 9.7 g. per 100 ml. (70% Haldane) is the lowest value acceptable as normal during pregnancy, but in our view that is too low, and for the purpose of this paper we have joined Elliott (1944) in accepting 11.04 g. per 100 ml. as our lowest normal figure.

Adair, Dieckmann, and Grant (1936) made a statistical analysis of many thousands of red cell counts, and concluded that 3.36 millions per c.mm. was the lowest level of the normal range. While we believe that this figure is too

low, we cannot accept the suggestion of Elliott (1944) that 4 millions per c.mm. is the nadir of the normal range, and we would suggest that where other measurements are normal (haemoglobin and M.C.V.) 3.5 millions per c.mm. may be regarded as normal.

The red cell counts in our cases remained normal by this standard, with the single exception of that done in the eighth month on Case 2. The haemoglobin levels fell below normal in the ninth month in Case 8, in the sixth and ninth months in Case 5, and from the seventh month until term in Case 12. In all these cases the red cell count remained within normal limits. Case 12 was treated for iron-deficiency anaemia at the eighth month of pregnancy.

Table II shows the M.C.V., the M.C.D., their standard deviation, and the variability percentage.

TABLE II.—M.C.V. in μ^3 , M.C.D. in μ , Standard Deviation (σ) and Variability Percentage (v) in Normal Pregnancy

Case No.	Value	Month of Pregnancy							
		2	3	4	5	6	7	8	9
1	M.C.V.			89	89	93	93	84	91
	M.C.D.			6.775	6.841	6.928	6.982	6.823	6.901
	σ			0.531	0.553	0.493	0.561	0.549	0.554
2	M.C.V.	86	95	87	94	88	90	93	81
	M.C.D.	6.832	6.828	6.693	7.000	6.825	6.719	7.227	7.137
	σ	0.505	0.514	0.581	0.625	0.625	0.561	0.588	0.651
3	M.C.V.	7.4	7.5	8.7	8.9	7.3	8.3	8.1	9.1
	M.C.D.					8.7	9.2	8.4	9.1
	σ					0.513	0.530	0.479	0.530
4	M.C.V.					7.3	8.3	6.8	7.4
	M.C.D.					8.6	9.5	9.4	9.3
	σ					0.537	0.526	0.524	0.519
5	M.C.V.					8.6	8.2	7.6	7.4
	M.C.D.					8.1	8.0	8.8	8.7
	σ					0.486	0.438	0.467	0.528
6	M.C.V.					7.04	6.4	6.8	7.9
	M.C.D.					8.5	9.1	8.3	8.6
	σ					0.509	0.526	0.526	0.508
7	M.C.V.					8.1	8.0	8.8	8.7
	M.C.D.					6.895	6.879	6.904	6.688
	σ					0.486	0.438	0.467	0.528
8	M.C.V.					7.04	6.4	6.8	7.9
	M.C.D.					8.5	9.1	8.3	8.6
	σ					0.509	0.526	0.526	0.508
9	M.C.V.					8.1	8.0	8.8	8.7
	M.C.D.					6.895	6.879	6.904	6.688
	σ					0.486	0.438	0.467	0.528
10	M.C.V.					7.04	6.4	6.8	7.9
	M.C.D.					8.5	9.1	8.3	8.6
	σ					0.509	0.526	0.526	0.508
11	M.C.V.					8.1	8.0	8.8	8.7
	M.C.D.					6.895	6.879	6.904	6.688
	σ					0.486	0.438	0.467	0.528
12	M.C.V.					7.04	6.4	6.8	7.9
	M.C.D.					8.5	9.1	8.3	8.6
	σ					0.509	0.526	0.526	0.508
13	M.C.V.					8.1	8.0	8.8	8.7
	M.C.D.					6.895	6.879	6.904	6.688
	σ					0.486	0.438	0.467	0.528
14	M.C.V.					7.04	6.4	6.8	7.9
	M.C.D.					8.5	9.1	8.3	8.6
	σ					0.509	0.526	0.526	0.508
15	M.C.V.					8.1	8.0	8.8	8.7
	M.C.D.					6.895	6.879	6.904	6.688
	σ					0.486	0.438	0.467	0.528
16	M.C.V.					7.04	6.4	6.8	7.9
	M.C.D.					8.5	9.1	8.3	8.6
	σ					0.509	0.526	0.526	0.508

The M.C.V. in pregnancy has been said to range from 77 to 100 μ^3 (Dieckmann and Wegner, 1934; Bethell, 1936; Watson, 1938). Elliott (1944) in a series of 20 normal women tested between the 10th and 38th weeks of pregnancy found an M.C.V. between 73 and 86 μ^3 . Our findings fell between 69 and 103 μ^3 . There appeared to be no obvious change occurring as pregnancy advanced.

Our range of M.C.D. was from 5.944 to 7.642 μ . Price-Jones gives the normal range of M.C.D. for non-pregnant women as 6.686 to 7.718 μ . Elliott (1944), who presents the only other published series of observations on M.C.D. in pregnant women with a haemoglobin of 11 g. per 100 ml. or more, measured the M.C.D. in 14 cases and found it to be between 6.7 and 7.7 μ . In none of our cases did there seem to be any degree of correlation between the M.C.V. and M.C.D. confirming the findings of Mogenson (1938), Schalm (1939-40), and Elliott (1944). In eight of our cases the M.C.D. was below Price-Jones's normal range on two or more occasions, and in one (Case 7) it was consistently below throughout pregnancy, despite the fact that her haemoglobin level, red cell count, and M.C.V. were well within normal limits throughout. Case 12 has not been included in the above eight because her haemoglobin began to fall after the sixth month and she was treated as a case of iron-deficiency anaemia; her M.C.D. fell below Price-Jones's normal range from the sixth month onwards.

Although there are statistically significant differences in the M.C.D. from month to month in the same individual pregnancy, these are found irregularly, and there seems to be no consistent tendency for the M.C.D. to increase or decrease significantly as pregnancy advances.

The variability percentage of the M.C.D. is usually taken as a statistical expression of the degree of anisocytosis. The upper limit of normal established by Price-Jones (1933) for healthy adults of both sexes is 7.3%. Our figures range from 5.87% to 9.86% and lie above 7.3% in 54 out of our 95 observations (56.7%). In no case was the variability percentage normal throughout pregnancy. There was no particular trend with regard to the variability percentage, abnormal findings being scattered throughout pregnancy.

Discussion

We believe that these are the first published observations on M.C.D. made serially on normal women throughout pregnancy. The analysis of our results shows that the M.C.D. of the red cells in pregnancy varies over a much wider range than in the non-pregnant individual. No fewer than 10 of our patients showed an M.C.D. of less than 6.686 μ (the lowest limit of normal given by Price-Jones) at one or more monthly examinations. In no case was it higher than normal. There is a definite tendency to increased anisocytosis in pregnancy even though the haemoglobin, red cell count, and M.C.V. are normal. There does not seem to be any correlation between abnormal microcytosis and anisocytosis. It is of interest to note that of Elliott's 20 normal patients 11 showed excessive anisocytosis.

Boycott (1936) has suggested that an abnormal degree of anisocytosis is a more important sign of abnormal haemopoiesis than any fall in haemoglobin level. If this is true our findings suggest that abnormal haemopoiesis is a feature of normal pregnancy. Since the M.C.D. tends to be low it is tempting to ascribe this to a dietary deficiency of iron. Moreover, Fullerton (1936) has calculated that the extra requirement of iron by the pregnant woman is not less than 2 mg. daily, and McCance *et al.* (1938) concluded that a satisfactory daily intake of iron during pregnancy would be 20 mg., an amount far higher than is usually supplied in most working-class or middle-class diets to-day. A dietary deficiency of protein might produce changes in the peripheral blood simulating an iron-deficiency anaemia.

Moreover, clinical experience shows that in pregnancy an anaemia which has all the features of iron deficiency in the peripheral blood can be associated with a megaloblastic

marrow reaction, and that this type of anaemia responds not to iron but to liver extract. It seems possible that the low M.C.D. associated with evidence of increased anisocytosis in pregnancy indicates a relative dietary deficiency, and that the increased stress of producing the material for the foetal red cells is shown in the altered architecture of the maternal erythrocytes—namely, a tendency to low M.C.D. with increased anisocytosis.

Summary

Serial estimations of haemoglobin, red cell count, mean corpuscular diameter, and mean corpuscular volume have been made during pregnancy in 16 healthy women.

The M.C.D. shows a greater range of variation than in healthy non-pregnant women.

There is evidence of abnormal haemopoiesis, indicating that a woman's diet is not completely adequate to supply the needs of both her own and the foetal red cells.

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DIRECT MICROSCOPICAL EXAMINATION OF FAECES IN INFANTS

BY

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The direct microscopical examination of a film of faeces has one great advantage over study of faeces by selective cultural media in that it affords a representative picture of the intestinal flora as a whole. The purpose of the present report is to record the results of such an examination of the faeces of infants both in health and in disease.

This investigation originated from a study of the problem of gastro-enteritis in infancy, of which an outstanding feature is its much greater frequency in artificially fed infants than in the breast-fed. Moreover, it has been shown by various workers that breast-fed infants have a decided advantage over bottle-fed infants in their resistance to infections of various kinds (Grulee, Sanford, and Herron, 1934; Cordua, 1935; Levi, 1941). During the past fifty years various attempts have been made to discover if any fundamental difference existed between the breast-fed and the artificially fed infant which might predispose the latter to infection, and especially to gastro-enteritis. In particular, the faeces have been extensively studied ever since Tissier, in 1900, demonstrated the pronounced difference between the intestinal flora of the suckling and the bottle-fed infant.