selective proteinuria," has rightly been criticized (de Wardener, 1967). This rather loose use of the term has been used to imply proteinuria which is the result of a highly selective process of filtration in the kidney. "Selected" and "poorly selected" proteinuria would be preferable, and since the investigation seems a useful one it is perhaps not too late to accept this or other agreed terminology which abuses the language less; the same reform is of course necessary in the terms used in defining renal histology, but at present it seems rather remote.

This summary is the result of co-operative work with a large number of persons. In addition to Drs. E. L. Becker, P. W. Sharpstone, and R. H. R. White, Dr. C. S. Ogg and Professor J. R. Trounce at Guy's have made major contributions. Without the co-operation of the many physicians and paediatricians who allowed the study of patients under their care, few data could have been collected. Mary-Jean Newton, Carol Sanders, Mike Miller-Jones, Mark Harvey, and Gabriel Bankole carried out most of the differential protein clearances with consistent skill.

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Folate Status throughout Pregnancy and in Postpartum Period

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Summary: The serial trends of the whole blood folate level in two groups of patients have been followed throughout pregnancy and up to six weeks postpartum. In those receiving iron alone the whole blood folate remained normal until the test at six weeks after delivery, at which time over half were in the deficient range. There appears to be a delay before this test reflects the current folate status when this changes rapidly. In those receiving iron plus 330 μg. of folic acid a day the results at this time were close to those at the beginning of pregnancy. Subnormal whole blood folate, red cell folate, and serum folate values occurred close to term in patients receiving iron alone, but were not found in those also receiving folic acid. Megaloblastic changes occurred at term in three patients receiving iron alone in whom the whole blood folate had repeatedly been low in early pregnancy.

The observations are consistent with the previous suggestion that 300 μg. of folic acid daily is a suitable supplement to prevent deficiency in late pregnancy and the puerperium.

Introduction

Previous investigations on the antenatal population in the industrial area of Glasgow have shown that, without folic acid supplementation during pregnancy, over a third of such patients develop subnormal postpartum serum folate levels (Willoughby and Jewell, 1966) and up to 3.4% manifest megaloblastic anaemia (Willoughby, 1967). From a comparison of the results after graded oral doses of folic acid in the range of 124 to 530 μg./day it was concluded that the increased requirements were in the region of 300 μg./day, this being deduced largely from the results of the postpartum serum folate levels.

The present investigation was undertaken to assess folic acid status by means of the whole blood folate level serially throughout the whole of pregnancy and the postpartum period in two groups of patients, one receiving iron alone and the other the same dose of iron but with the addition of 330 μg. of folic acid a day. The reason for determining the whole blood folate level in the present investigation was that this measurement largely depends on the red cell folate level, since there is close to a 50 times higher concentration in the cells than in the plasma, and it has been suggested that the red cell folate levels reflect the tissue stores of this vitamin more accurately than do the serum folate levels (Hansen, 1964; Hoffbrand, Newcombe, and Mollin, 1966). The latter, being more labile, are more susceptible to extraneous metabolic influences than the intracellular levels.

In addition the basal fasting serum folate and the calculated red cell folate values were determined in the immediate postpartum period, at which time it may reasonably be assumed that the maximum demands on folate stores will be operative. These measurements have been correlated with serial haemoglobin estimations throughout pregnancy and with additional morphological assessment of the peripheral blood in the immediate postpartum period with the object of detecting those patients developing anaemia or overt megaloblastic changes.

A further object of the present investigation was to assess the possible value of the whole blood folate measurement as a means of predicting early in pregnancy those patients more liable to develop overt folic acid deficiency later in pregnancy, as has been shown to be the case in patients with initially low serum folate levels (Temperley, Meehan, and Gatenby, 1968).

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Clinical Material and Methods

Sixty-eight patients making their first antenatal attendance were randomly allocated to a group receiving 195 mg. of elemental iron a day, as three tablets of Fersamal, and a group receiving the same iron plus 300 μg. of folic acid a day, as three tablets of Pregamal. Four patients were removed by the obstetricians from each of the two treatment groups because of irregular consumption of tablets. Six patients aborted after their first visit. Six patients were excluded because they were being given other haematinic tablets. Thus 48 patients remained for subsequent analysis. None of these were twin pregnancies. The allocation code was not broken until all haematological assays and assessments had been completed. According to information from the Analytical Department of Glaxo Ltd. the tablets containing an intended 300 μg. of folic acid daily in fact contained 330 ± 30 μg.

At every antenatal and postnatal visit a finger-prick haemoglobin and whole blood *Lactobacillus casei* folate estimation was performed. At delivery the haematinic tablets were temporarily discontinued and between the second and fourth days after delivery venous blood was collected three hours after breakfast for serum *L. casei* folate, serum vitamin B_{12}, haemoglobin, haematocrit, and morphological assessment of the peripheral blood according to the methods and criteria described previously (Willoughby and Jewell, 1966). Whole blood folate assays were performed by the technique of Strelling, Blackledge, Goodall, and Walker (1966) as described previously (Willoughby, 1967).

There were a number of defaults in that 19 patients failed to attend at their six-week postnatal visit and that in 14 instances the full postpartum haematological measurements were not made. These errors were apparently random and are unlikely to affect the results.

Healthy normal non-pregnant young women associated with the department were similarly tested approximately three hours after their breakfast in order to determine the comparable normal range of whole blood folate, serum folate, and red cell folate levels. These assays were performed contemporaneously with investigations on the above-mentioned patients. The results were similar but not identical to those reported by other workers (Izak, Rachmilewitz, Sadovsky, Bercovici, Aronovitch, and Grossowicz, 1961 ; Hoffbrand *et al.*, 1966 ; Varadi, Abbott, and Elwis, 1966).

Over the period of this investigation (March 1967 to January 1968) other patients were encountered in whom a diagnosis of megaloblastic anaemia of pregnancy was made, the criteria previously discussed being used (Willoughby and Jewell, 1966). The serum folate, whole blood folate, and red cell folate results in this group of patients have been used in an attempt to define the ranges found in folic acid deficiency of pregnancy and the puerperium.

The whole blood folate results show a more clear-cut distinction between the normal and the megaloblastic group of patients than do the serum or red cell folate results (Figs. 1 and 2). This is partly spurious, since the presence of anaemia reduces the whole blood folate, but not the other two assays, by virtue of the fact that the red cells are the major source of the whole blood folate activity. With this reservation, however, it can be said that a " normal " or high whole blood folate result is valid and likewise a " low " whole blood folate result in the absence of anaemia. Since, as described below, anaemia was rare in the patients under investigation the serial trends among these patients were therefore meaningful. This was particularly so at the six-weeks postpartum test, at which time no patient had a haemoglobin concentration less than 12.3 g./100 ml.

Statistical methods were as described in *Documenta Geigy* (1956). Median values of folate assay results have been plotted, since these may be more meaningful than the mean values where there is a skew distribution, as pointed out by Lowenstein, Cantlie, Ramos, and Brunton (1966).

Results

Fig. 1 shows the scatter of whole blood folate values in the two groups of patients, either on iron alone or on iron plus folic acid, at representative stages of their antenatal and postnatal periods. The first antenatal visit was between 9 and 20 weeks' gestation (mean 12 weeks), the approximate seventh month visit was between 28 and 32 weeks (mean 30 weeks), the pre-delivery test was at the last antenatal visit before delivery (35–43 weeks, mean 38½ weeks), the puerperium test was two to four days after delivery, and the postnatal was approximately six weeks after delivery. The mean and median whole blood folate values are shown for each group of tests. The results in a group of normal non-pregnant young women and also in a group of patients encountered with megaloblastic anaemia of pregnancy or the puerperium are set out in a similar manner (under " controls ") to facilitate comparison with the results from the two groups of patients. A line has been drawn through the figure corresponding to a whole blood folate value of 60 mμg./ml., since it is thought that this is approximately the lower limit of normal and that results below this value indicate some degree of folate depletion. The results in three patients developing megaloblastic changes in the puerperium are indicated by a " boxed " symbol.

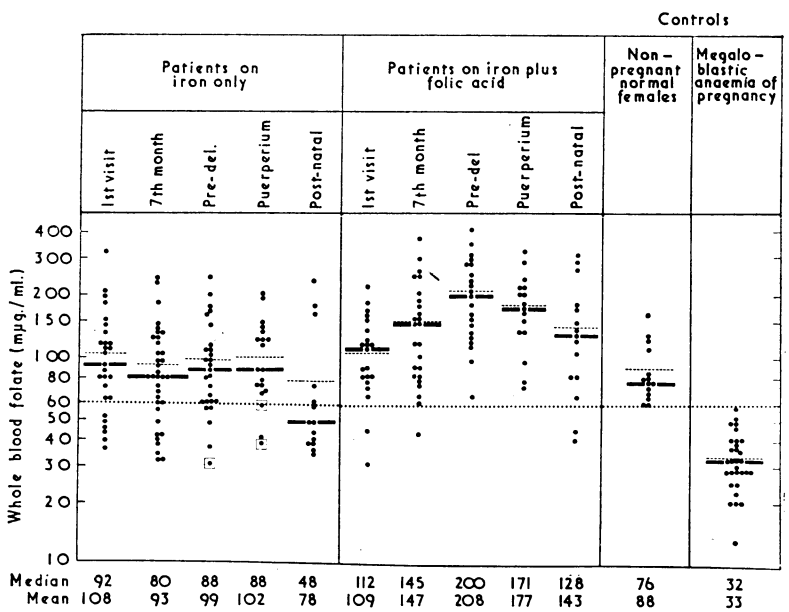

FIG. 1.—Whole blood folate levels during and after pregnancy. —— Median value. - - - - Mean value. □ Patient developing megaloblastic anaemia.

It can be seen from Fig. 1 that the median and mean whole blood folate levels remained close to normal throughout pregnancy and the immediate puerperium but fell to subnormal by six weeks after delivery in the patients receiving iron alone. In those having iron plus folic acid these values gradually rose to supranormal levels at the end of pregnancy but thereafter fell so that by the sixth postpartum week the median figure was close to that at the first visit—that is, before folic acid supplements were begun. Also it can be seen from Fig. 1 that a much higher proportion of those patients on iron alone developed subnormal whole blood folate levels than did those on iron plus folic acid. By six weeks after delivery 9

out of 14 results were less than 60 mμg./ml. in the first group, compared with 2 out of 15 in the second. Whether evaluated by "contingency tables," scoring the numbers below 60 mμg./ml. in the two groups, or by testing the differences of the means, these two sets of results are statistically significant ($\chi^2=8.0$, $P<0.01$; $t=2.36$, $P<0.05$).

Fig. 2 similarly shows the scatter of red cell folate and serum folate concentrations in the same two groups of patients, but only in the immediate postpartum period. Iron and folic acid were withheld for four days after delivery, and the "fasting" serum folate level was estimated at the same time, two to four days after delivery, as the haematocrit and whole blood folate, so as to calculate the red cell folate by the formula:

$$\text{R.B.C. folate} = \frac{\text{whole blood folate} - \text{serum folate}\ (1 - \text{P.C.V./100})}{\text{P.C.V./100}}$$

(Hoffbrand *et al.*, 1966). As in Fig. 1, the results from the same normal controls and some patients with megaloblastic anaemia of pregnancy or the puerperium are shown for comparison. A line has been drawn at 150 mμg./ml. to indicate the approximate lower limit of normal in this area. The results in patients showing megaloblastic changes have been given a "boxed" symbol.

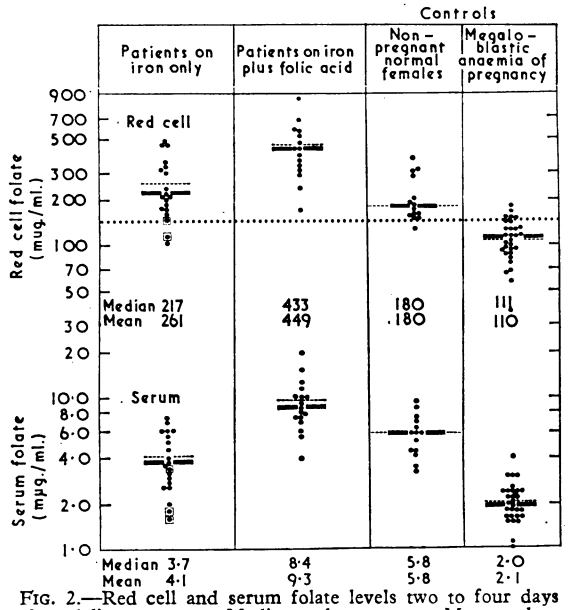

FIG. 2.—Red cell and serum folate levels two to four days after delivery. —— Median value. ---- Mean value. ☐ Patient developing megaloblastic anaemia.

It can be seen from Fig. 2 that the postpartum red cell folate concentration in patients receiving iron only are on average slightly above the normal non-pregnant controls, but that two results are lower than normal, these being close to the mean of the patients with megaloblastic anaemia, and that of these two patients one had megaloblastic features; one in fact with circulating late megaloblasts in the peripheral blood (Table II).

The average red cell folate concentration in patients receiving iron plus folic acid is seen to be above normal in the immediate postpartum period, since the mean and median values of this group are higher than any of the normal controls. None of the results are in the subnormal range.

Unlike the red cell folate the serum folate levels in the "iron only" group were more frequently in the deficient range, less than 3 mμg./ml., than were the normal controls ($\chi^2=5.1$, $P<0.05$), two of these low values being associated with megaloblastic changes in the blood. The patients given iron plus folic acid had somewhat higher results than the normal controls. None was in the deficient range, the lowest result being 4 mμg./ml. four days after stopping oral supplementation.

Table I shows the initial, pre-delivery, immediate postpartum, and six-weeks' postnatal mean haemoglobin concentrations. It is seen that initially the group given iron alone was well matched as regards haemoglobin level (as well as mean whole blood folate levels, which were 108 and 109 mμg./ml. respectively. The mean haemoglobin values fell slightly but were identical at two to four days after delivery, subsequently rising to above their initial levels by six weeks. Out of 460 tests on these 48 patients throughout the period of investigation the results were below 11 g./100 ml. on 22 occasions—five of these being in the patients with megaloblastic changes—and below 10 g./100 ml. on three occasions, these being also in a patient with megaloblastic changes.

TABLE I.—*Mean Haemoglobin Levels, Serum Vitamin B_{12}, and Percentage of Hypersegmented Polymorphs*

	Haemoglobin (g./100 ml.)				Post-partum Serum B_{12}	Postpartum Hypersegmented Polymorphs*
	Initial	Pre-delivery	Post-partum	Post-natal		
Patients on iron alone ..	13·4	12·7	12·6	14·2	230 μμg./ml.	7·5%
Patients on iron + folic acid	13·2	13·4	12·6	14·7	230 μμg./ml.	4·5%

* Containing five or more nuclear lobes.

The postpartum serum vitamin B_{12} level was identical in the two groups.

The average percentage of hypersegmented polymorphs—that is, with five or more lobes—was higher in the group of patients without folic acid supplementation, but the difference was not statistically significant.

Among the 27 patients on iron alone three developed morphological evidence of megaloblastic changes in the immediate postpartum period. These are the patients referred to by "box" symbols in Figs. 1 and 2. Further details, both

TABLE II.—*Serial Whole Blood Folate (W.B.F.) Levels in Three Patients Subsequently Showing Megaloblastic Changes*

Case No.	Gestation in Weeks (approximately)										W.B.F.	Hb	Serum Folate	R.B.C. Folate	Serum B_{12}	Morphology
	10	14	22	26	30	34	36	38	39	40						
1	45	—	20	24	32	36	Delivery				—	9·6	1·6	—	100	Macrocytes, H.P., H.-J.B.
2	49	—	46	64	64	64	68	72	—	56	38	10·2	1·8	115	200	Macrocytes, H.P., H.-J.B., megaloblasts
3	[illegible]	148	56	—	42	104	[illegible]	78	94	92	58	11·6	3·4	160	250	Macrocytes H.P., H.-J.B., macropolycytes
4*	85	—	40	84	160	136	—	—	—	—	192	14·2	6·8	425	400	Normal

H.P. = Hypersegmented polymorphs. H.-J.B. = Howell-Jolly bodies.

* This patient was initially given iron alone but was inadvertently changed to iron plus folic acid supplementation at 21 weeks' gestation.

R.B.C., whole blood, and serum folate in mμg./ml., serum B_{12} in μμg./ml., Hb in g./100 ml.

No other patients developed these megaloblastic features. Seven other patients had two or more low whole blood folate tests and eight other patients had a single ow whole blood folate test.

with regard to the evidence that they were cases of "megaloblastic anaemia of pregnancy" (in the absence of marrow examination) and with regard to their preceding levels of whole blood folate over the months before this development, are shown in Table II. The whole blood folate levels anticipated the development of anaemia.

To Table II are appended the results in a patient (Case 4), initially on iron alone, who was inadvertently changed to iron plus folic acid at 21 weeks' gestation. Though this case is removed from the cases for analysis the subsequent upward trend of whole blood folate levels, compared with the other three cases, is of interest.

Discussion

These results confirm the previous findings (Willoughby and Jewell, 1966; Willoughby, 1967) that, in the antenatal population of Glasgow, evidence of folic acid deficiency is found in a significant proportion of patients after delivery unless folic acid supplements are given in addition to iron, and that 330 μg. of oral folic acid a day is adequate in preventing the occurrence of this deficiency in the majority of such patients. The present investigation differs from the previous ones in that serial whole blood folate estimations throughout pregnancy, and red cell folate determinations in the postpartum period, have been included in assessment of the patients' folate status. Low whole blood folate levels have been more frequent in those receiving iron alone (Fig. 1) and have been associated with the development of megaloblastic anaemia in three instances in this group. Low red cell folate levels of 105 and 115 mμg./ml., one of which was associated with megaloblastic anaemia, have been found in the immediate postpartum period among the 27 patients receiving iron alone (Fig. 2). No instances of subnormal serum, whole blood, or red cell folate nor morphological evidence of megaloblastic change have been found among the 21 patients receiving iron plus 330 μg. of oral folic acid a day when tested two to four days after delivery (Figs. 1 and 2).

An unexpected finding in the present investigation is that it is not until the tests at six weeks after delivery that there is a fall in the mean or median values of the whole blood folate (Fig. 1) and, by implication, of the red cell folate level in the patients receiving iron alone even though the serum folate level is lower (Fig. 2) and the percentage of hypersegmented polymorphs in the blood is higher (Table I) some 5½ weeks earlier—namely, at the time of tests two to four days after delivery. The median red cell folate concentrations at this immediate postpartum period was in fact slightly higher than that in normal non-pregnant controls (Fig. 2).

If it were not for the fact that there is a subsequent marked fall in whole blood folate levels over the six weeks following delivery (Fig. 1) it would have appeared that this most precise measurement of folate status—namely, the red cell folate concentration—was failing to substantiate the hypothesis that folate depletion is common among this population in late pregnancy.

Similarly the abnormally high whole blood folate levels in late pregnancy and red cell folate levels after delivery in the folic-acid-supplemented group of patients would suggest that the supplement of 330 μg./day is considerably in excess of requirements were it not for the subsequent fall in whole blood folate levels. By six weeks after delivery these levels in the folic-acid-supplemented group are again down to a median value of 128 mμg./ml., which is close to the initial pretreatment figure of 112 mμg./ml. in this same group of patients.

The intracellular concentration of folate, on which the whole blood folate largely and the red cell folate level wholly depend, is thought to reflect the erythropoietic folate stores at the time the respective red cells are generated in the marrow (Hoffbrand *et al.*, 1966). Their subsequent life-span in the circulation is approximately 110 days, with linear destruction in the absence of blood loss (Mollison, 1961). The red cell folate appears to be stable (Hansen, 1967). The circulating population of red cells and their folate content pertain, therefore, to an earlier stage of pregnancy, on average two to three months earlier, rather than to the time at which they are tested (Streiff and Little, 1967). This makes it likely that if the maximum folic acid requirements occur in, say, the last month of pregnancy any erythropoietic depletion resulting thereby would not be maximally reflected by the red cell or whole blood folate levels until several weeks after delivery. It is therefore entirely understandable that the whole blood folate level was low, with a median value of 48 mμg./ml. six weeks after delivery in the group of patients receiving no folic acid supplement.

In those patients receiving 330 μg. of folic acid a day the median value of 128 mμg./ml. at six weeks after delivery was close to the initial pretreatment value of 112 mμg./ml., suggesting that this supplement just covered the average increased requirements in late pregnancy. The serum folate levels, being independent of the length of red cell survival, gave evidence of deficiency in the immediate postpartum period in the former group of patients, but not in the folic-acid-supplemented group, as had been found in the previous investigation (Willoughby and Jewell, 1966).

Support for this concept was found by correlating the immediate postpartum serum folate and the six-weeks' postnatal whole blood folate levels in the same patients. There was a significant correlation between these values (correlation coefficient 0.635, $t=3.675$, $P<0.01$). Also the three patients with the lowest postpartum serum folate levels subsequently showed the three lowest whole blood folate levels.

The supranormal whole blood folate levels found at term in the folic-acid-supplemented group appear in this light to indicate that 330 μg. is in excess of daily requirements during the preceding months of pregnancy, dating from the 12th week, but is not necessarily in excess of the requirements in late pregnancy or at delivery.

This, similarly, may be the explanation that Hansen and Rybo (1967) found 100 μg. adequate and 200 μg. more than adequate; and Chanarin, Rothman, Ward, and Perry (1968) found 100 μg. adequate. They tested the whole blood folate or red cell folate before delivery in each case.

Aside from the use of the whole blood folate assay in the above investigation it was hoped that this test might also provide a simple screening procedure for detecting early in pregnancy those patients at particular risk with regard to the subsequent development of megaloblastic anaemia in late pregnancy or the puerperium. From the above discussion this test would appear to reflect the folate stores during the immediately preceding months (but would be slow to show a phase of acute folate depletion in late pregnancy).

Details of the three patients who showed megaloblastic changes after delivery are shown in Table II. It can be seen that low whole blood folate levels anticipated the development of postpartum megaloblastic anaemia by many months and that the test had therefore proved useful in detecting those patients at particular risk. Presumably these three patients entered pregnancy with low folate stores and were later unable to meet the increased demands that arose close to the time of delivery. Chanarin *et al.* (1968) reported a similar observation. In one patient (Case 4) with a similar low level of whole blood folate early in pregnancy a change to folic acid tablets (330 μg./day) resulted in a gradual correction of the whole blood folate level and normal blood findings after delivery. The incidence of folic acid deficiency in the first trimester has

been found to be greater than was previously thought (Stone, Luhby, Feldman, Gordon, and Cooperman, 1967), sometimes no doubt owing to the slow return to normal of folate status following a previous pregnancy (Temperley *et al.*, 1968). This sequence of events could occur if those patients on iron alone and with low postnatal whole blood folate levels soon became pregnant again.

Conclusions

Folate depletion in late pregnancy is again found to be common when assessed by the whole blood folate level, but only when this is tested some weeks after delivery, because of the delay in its reflection of folate status.

This depletion is prevented by the prophylactic administration of 330 μg. of folic acid a day, and the whole blood folate level six weeks after delivery is then close to the initial pre-treatment levels in early pregnancy in this group of patients.

Though the whole blood folate is slow to reflect changes in folate status (compared with the serum level) it is a valid index of this in that a low value in early pregnancy indicates an increased liability to development of overt megaloblastic changes in late pregnancy.

We gratefully acknowledge the co-operation of Professor I. Donald, Drs. J. M. McBride, W. Barr, J. Willocks, and J. MacVicar during the conduct of this investigation, together with the help we have received from Miss McLeod and her staff in the antenatal clinic, Mr. R. Ferguson and his staff in the random allocation of patients, and Mrs. M. Shanks in the abstracting of information from case records. We are also indebted to Glaxo Ltd. for information concerning the folic acid content of Pregamal tablets.

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Circulatory and Metabolic Effects of Oxygen in Myocardial Infarction

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Summary: The circulatory and metabolic effects of inhalation of oxygen in high concentration were investigated in 50 patients with acute myocardial infarction. The heart rate, arterial blood pressure, cardiac output, blood gas tensions, pH, and lactate and pyruvate levels were measured. In general, oxygen inhalation produced a fall in cardiac output and stroke volume and a rise in blood pressure and systemic vascular resistance. In a small number of patients with very low cardiac outputs there was a rise in output. A substantial rise in arterial oxygen tension was obtained even in patients with low initial values. The raised arterial blood lactate levels which were frequently present were reduced after oxygen. The therapeutic implications of these effects are discussed.

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Introduction

The circulatory disturbances associated with myocardial infarction have recently been the subject of several detailed studies (Broch *et al.*, 1959; Malmcrona and Varnauskas, 1964; Thomas *et al.*, 1965a). In addition to haemodynamic changes, one of the important findings has been a reduction in arterial oxygen tension, especially in the presence of left ventricular failure and cardiogenic shock (MacKenzie *et al.*, 1964; McNicol *et al.*, 1965; Valentine *et al.*, 1966). Hypoxia may be largely responsible for some of the serious metabolic abnormalities which take place and may also contribute to the production of hypotension. Though administration of oxygen has long been recommended in the management of myocardial infarction (Dunlop and Alstead, 1966; Friedberg, 1966) there is little information available concerning its effects on the underlying circulatory derangements (MacKenzie *et al.*, 1964; Thomas *et al.*, 1965b; Cameron *et al.*, 1966). The object of the present investigation, therefore, was to determine the haemodynamic and metabolic effects of the administration of oxygen in high concentration to patients with myocardial infarction and to assess its therapeutic value.