CHANGES IN BLOOD VALUES DURING PREGNANCY AND THE RELATION OF PROTEIN LEVELS TO TOXEMIA SYMPTOMS[1]

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CHANGES in the concentration of various constituents in the blood during pregnancy must be considered in relation to the well-known increase in plasma volume. Therefore, as a background for this report on hematological values and serum protein levels obtained for prenatal ward patients in the Study on The Relation of Nutrition to Pregnancy, now in progress at the Pennsylvania Hospital, some data will be presented from two studies on the increase in plasma volume during pregnancy.

In a recent report, Caton and others (1) published for ten patients at the Boston Lying-In Hospital the results of serial observations on prenatal and postpartum plasma volume and volume of red blood cells (hematocrit). Of these, one was a mild pre-eclamptic and one had a premature birth. From the estimates of total plasma volume for the eight presumably normal cases reported at four to seven antepartum periods for each patient and a postpartum value taken 26 to 66 days after delivery, the average per cent by which the antepartum plasma volume exceded the postpartum volume was calculated for six different antepartum periods.[3] The estimated curve for

[1] This is a preliminary report on data from a Study on The Relation of Nutrition to Pregnancy, being conducted at the Pennsylvania Hospital (Philadelphia Lying-In Hospital), Philadelphia, under the direction of Dr. Winslow T. Tompkins. The Study is receiving support from the Milbank Memorial Fund, the Williams-Waterman Fund, the National Vitamin Foundation, the Nutrition Foundation, the Upjohn Company, Mead Johnson and Company, E. R. Squibb & Sons, and Mulford Colloidal Laboratory.

[2] The Milbank Memorial Fund, statistical consultant to the Study.

[3] Determinations of total plasma volume were not made at uniform periods of pregnancy for all cases, but most of the observations could be grouped in periods having a three-week range. In order not to widen the range nor to omit cases, several values used were interpolations between two observations made at an earlier and later week of gestation. The average for the final period before delivery is for 0 to 11 days. For one of the eight patients the earliest antepartum plasma volume (11 weeks of gestation) was 5 per cent less than the postpartum plasma volume, and for this case the earliest antepartum volume was taken as the base from which the percentage increase was computed.

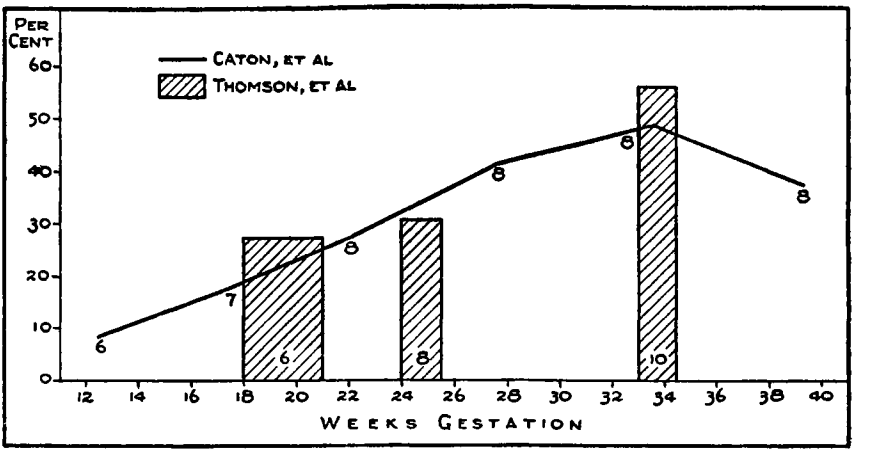


Fig. 1. Percentage increase in total plasma volume during pregnancy over postpartum plasma volume estimated from data published by Caton, *et al.* (1) and from Thomson, *et al.* (2). Numbers indicate number of determinations on which average increase is based.

plasma volume increase obtained from these data is shown in Figure 1. The curve rises from 9 per cent at about 12 weeks of gestation to 48 per cent at 33 weeks, then decreases in the last ten days before delivery to 37.5 per cent.

On the same chart the three bars show the average per cent above postpartum plasma volume calculated[4] from data published by Thomson, *et al.* (2). The two studies do not differ significantly when the small number of cases and variation among individual patients are considered.

The wide differences among patients in the changes in plasma volume during pregnancy are apparent from the individual curves plotted in Figure 2 for the eight cases studied by Caton, *et al.* The maximum antepartum volume exceeded the postpartum volume by 36 to 72 per cent and always occurred in the third trimester. The plasma volume decreased significantly

[4] The average percentages for excess in plasma volume during pregnancy over the postpartum plasma volume shown in Figure 1 for the data from Thomson, *et al.* are based on a total of eleven cases for which one to four antepartum plasma values were reported. One case with anemia and edema was excluded. The average percentages are for a range of 3 weeks at 18 to 20 weeks of gestation, a range of 11 days at 24 to 25 weeks of gestation for six of the eight cases included, and a range of 10 days at 33 to 34 weeks of gestation for six of the nine cases included. Postpartum plasma volume was at 11–14 days after delivery for eight cases; at 20, 43, and 68 days for the other three.

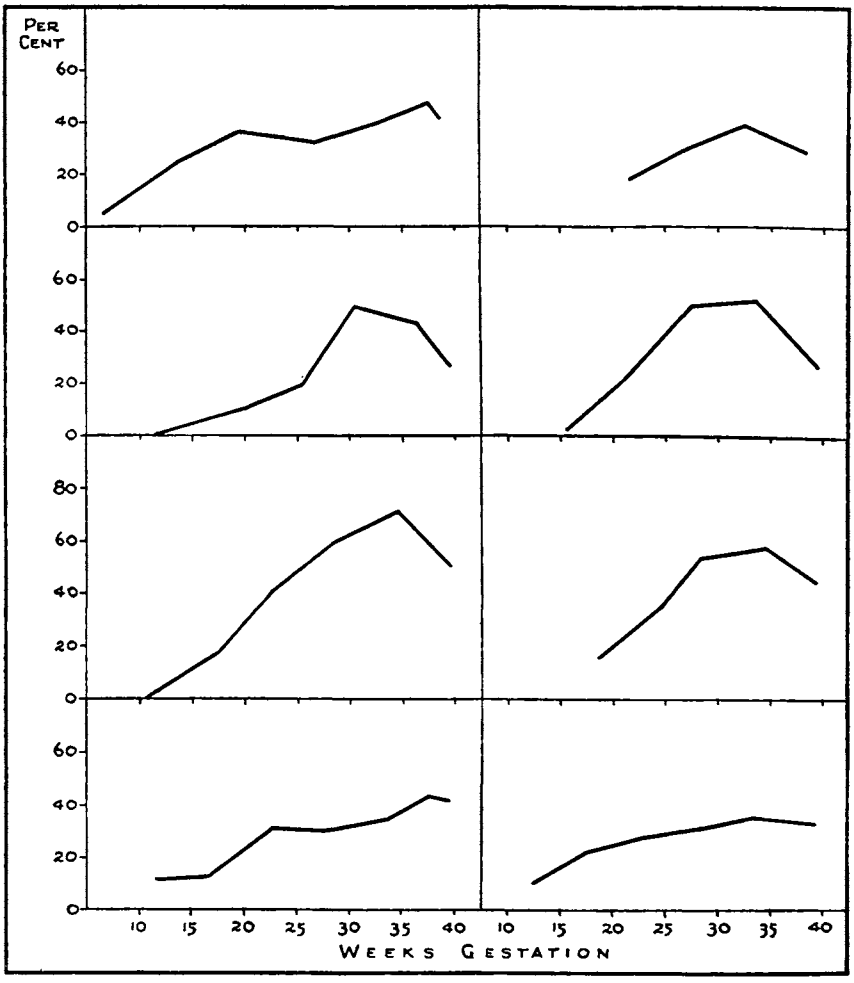


Fig. 2. Individual curves for percentage increase in plasma volume during pregnancy for eight women studied by Caton, *et al.* (1).

before delivery in five of the eight cases. It is apparent that some cases had shown little or no increase in plasma to the end of the first trimester, but for one case plasma volume at 13 weeks was 25 per cent above the postpartum value and was 5 per cent above at 6 weeks. In general, there seems to be a sharp increase in plasma volume throughout the second trimester and during the first half of the third trimester, after which the plasma volume tends to remain constant or to decrease.

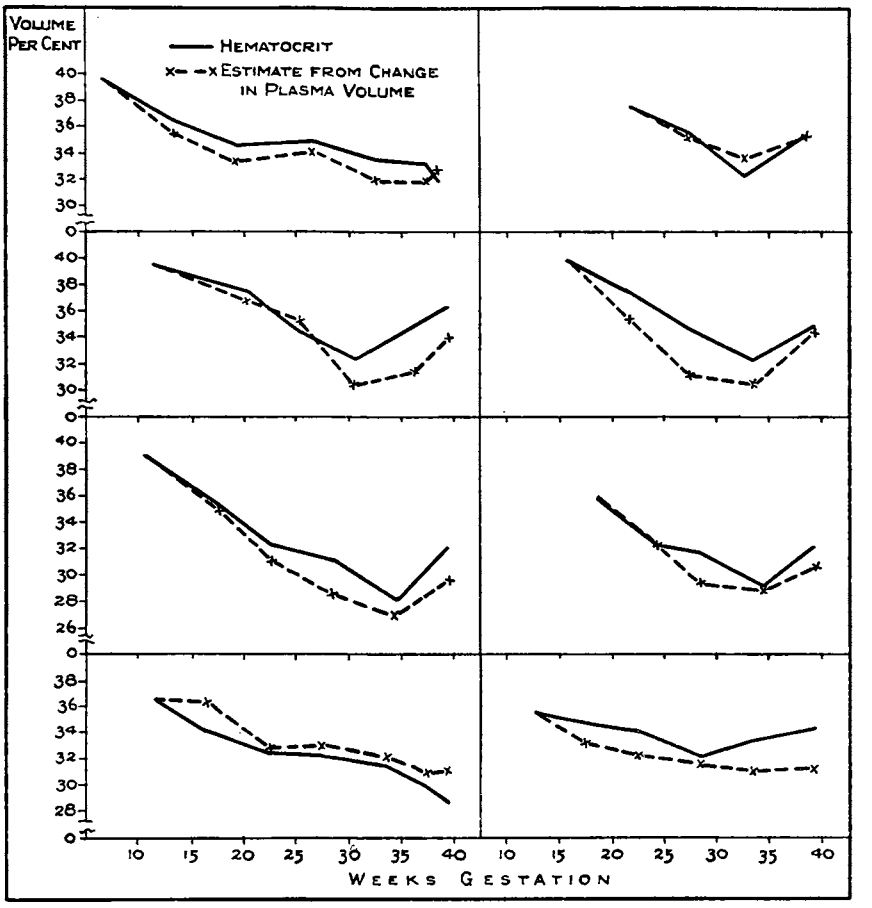


Fig. 3. Hematocrit values obtained during pregnancy for eight women studied by Caton, *et al.* (1) compared with changes in hematocrit values from first determination that would be expected as result of the observed individual plasma volume changes.

If no change in the total volume of circulating red cells occurs, the hematocrit could be expected to decrease in proportion to the dilution caused by the increase in plasma volume. In Figure 3, the reported hematocrits for the eight cases are shown together with the hematocrits that might be expected as a result of the observed increase in plasma volume. For each case the reported total plasma volume and hematocrit for the earliest period in pregnancy is used as a base and each later hematocrit is estimated by computing the hematocrit

expected for the change in plasma volume between the earliest period and a later period.

Two generalizations are suggested by Figure 3. First, the fluctuations in the observed hematocrits from one period to the next follow fairly closely the upward and downward changes in the estimated expected hematocrit.[5] Second, there is a definite tendency for the expected hematocrits to be lower than the observed, that is, the actual decrease in the percentage of red cells in the blood was less than expected as a result of dilution on account of plasma increase. The same tendency for higher hematocrit values than the estimated expected hematocrits was found for the patients studied by Thomson, *et al.* Thus, these two studies have given evidence that the production of red cells increased during pregnancy, though not in an amount sufficient to completely compensate for the increased plasma volume.

Trends in Blood Values

The change in the average hematocrit values and in the hemoglobin levels during pregnancy is shown in Figure 4 for 161 white women in the Study at Philadelphia Lying-In Hospital. The broken lines are the average values expected if the levels before and after 17 weeks of gestation[6] had varied in proportion to the average change in plasma volume shown by the data from Caton, *et al.*

From 12 to 17 weeks of gestation both hematocrit and hemo-

[5] Each estimated hematocrit is affected by the accumulated errors of two plasma volume determinations (the earliest and a later value) and of the earliest hematocrit reading. The curves obtained for the estimated hematocrit values suggest a high degree of accuracy for the plasma volume determinations. The one case for which the expected hematocrit values were consistently higher than the observed hematocrit values could result from error in the earliest determination of either the plasma volume or hematorcrit. If the second period (16 weeks of gestation) is used as a base, the usual *lower* estimate than observed hematocrit is obtained.

[6] The expected average levels in the blood constituents are estimated from the observed level at 17 weeks because nearly all women included in the group for which average curves were obtained were observed at 16–18 weeks of gestation and also because the average plasma volume increase at this period was more reliable statistically than the average at 12 weeks. The weeks of gestation used for all cases except those resulting in premature births (5.5 lbs. or less) are computed from date of delivery using delivery date as 280 days.

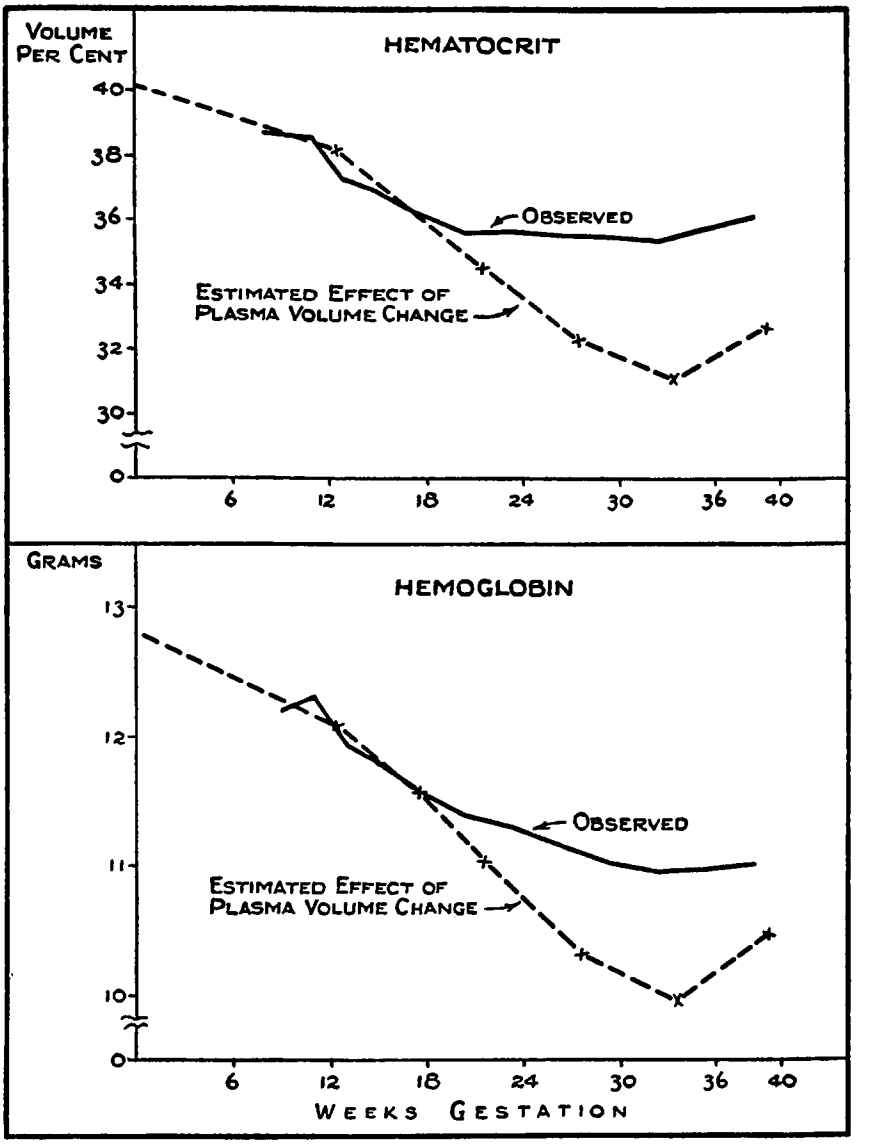


Fig. 4. Average hematocrit and average hemoglobin values during pregnancy for 161 white ward patients at Pennsylvania Hospital and average levels expected on basis of percentage plasma volume change before and after 17 weeks of gestation.

globin values decrease quite rapidly and the amount of the decrease is very close to that estimated from plasma volume change.

After 20 weeks of gestation there is almost no further decrease in the observed hematocrit values and there is a slight increase in the final six weeks of pregnancy. It is apparent that whatever increase in plasma volume occurred for this group of women, it was offset on the average by an increase in red cells during the latter half of pregnancy.

The average hemoglobin curve differs from the hematocrit curve in that it continues to decline to the 31st week of gestation and the terminal increase in hemoglobin is very slight. However, the decrease in hemoglobin also is much less than that estimated as expected from dilution of the value by increase in plasma volume. The greater decrease in hemoglobin than in volume of packed red cells shows the effect on the average curves of the hypochromia found for many women during pregnancy. Thus, although there is apparently an increased production of hemoglobin as well as of red cells, it is not sufficient in many cases to maintain the normal concentration of hemoglobin in the cells.

The changes in total serum protein, albumin, and globulin during pregnancy are shown in Figure 5. Again, the broken lines show the changes expected if the total protein, albumin, and globulin levels had varied in proportion to the dilution that would result from the increased plasma volume if no change in amount of protein or its fractions occurred. The expected values for protein are estimated from the averages at 12 weeks of gestation using the percentage decrease expected from the percentage increase in plasma volume after 12 weeks.[7]

The average curve for the total protein decreases from 7.1 grams at about 8 weeks of gestation to 6.65 grams at 16–18 weeks, and thereafter shows little change with a minimum level of 6.5 grams at 31–33 weeks. The average values for serum

[7] The average plasma volume change from 12 to 17 weeks of gestation has been shown to fit very closely the change in hematocrit and hemoglobin values, and therefore the plasma volume at 12 weeks seems to afford as satisfactory a base for estimating expected changes in blood constituents as the value for 17 weeks. Since globulin starts to rise after 12 weeks of gestation, the comparison of observed levels with expected levels is better if the two curves are brought together at 12 weeks or earlier.

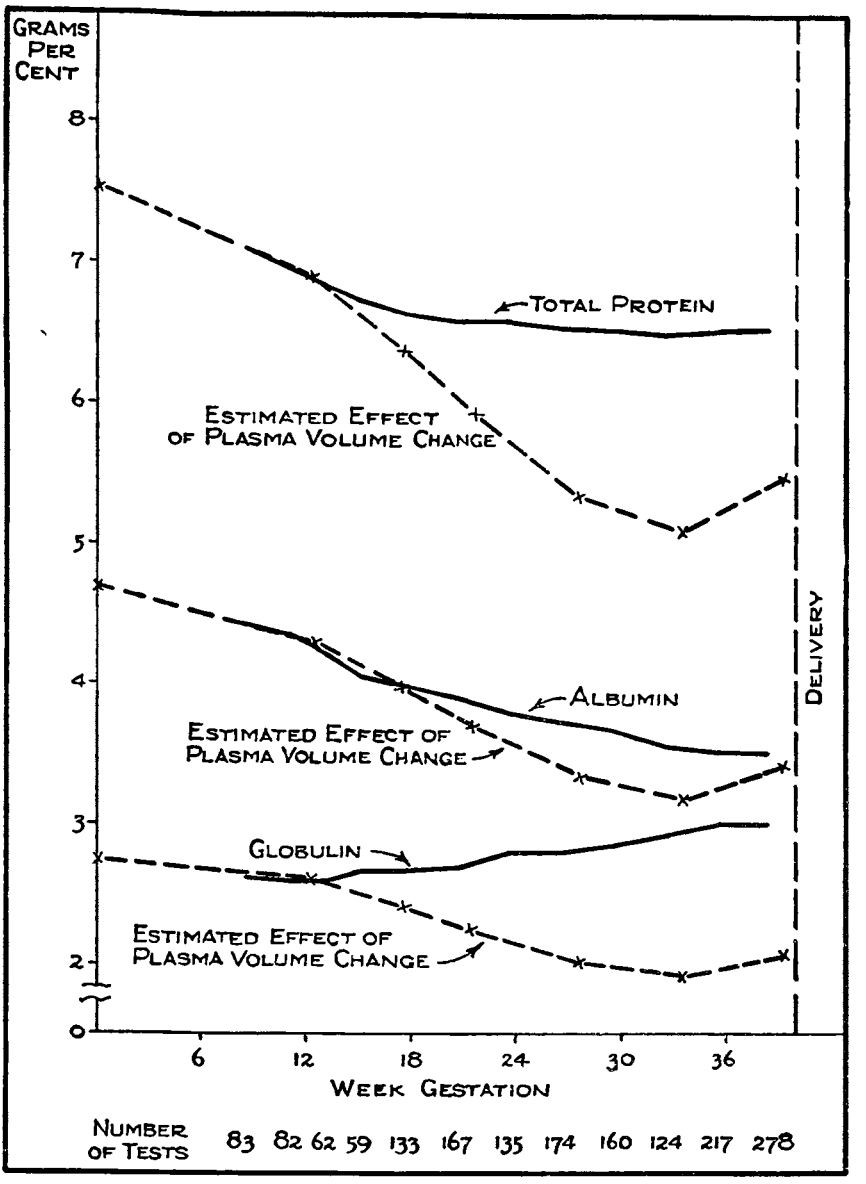


Fig. 5. Average total serum protein, serum albumin, and serum globulin for white ward patients at the Pennsylvania Hospital, Nutrition Research Clinic, and average levels expected on basis of percentage plasma volume change before and after 12 weeks of gestation.

albumin, however, decreased throughout pregnancy, declining from 4.4 grams to 3.5 grams. At the lowest level the decrease

in serum albumin is, on the average, about 70 per cent of the decrease from the level at 12 weeks expected as a result of plasma volume dilution.

Serum globulin increases steadily during the second and third trimester of pregnancy. This increase is sufficient to offset the decrease in albumin after about 20 weeks of gestation and, as noted already, to maintain total serum protein at a fairly constant level during the latter half of pregnancy. At a level of 3.0 grams in the last six weeks of pregnancy the serum globulin level is above the estimated pre-pregnancy level and represents an increased production of globulin of about 57 per cent, if we accept the plasma volume increase shown by the data from Caton, *et al.* as valid for the Philadelphia women. The albumin level at the end of pregnancy, on the other hand, is 25 per cent below the pre-pregnancy level, although the serum concentration maintained at the minimum level would have required an increased output of albumin of 10 per cent. The net increase in total circulating protein over the estimated pre-pregnancy amount is between 25 and 30 per cent.

Albumin is needed during pregnancy to build new tissue for the placenta and the fetus, and it must be withdrawn from circulation in considerable amounts. Therefore, the actual increase in production of albumin is presumably greater than the 10 per cent estimated for the maintenance of the observed serum concentration. The demand for total protein levels that will maintain a satisfactory physicochemical balance apparently is met by a marked increase in globulin. A recent experiment by Miller (3) on dogs using tagged DL-Lysine showed that plasma globulin was synthesized more rapidly than albumin. Under the stress of pregnancy a rapid synthesis of globulin seems to be stimulated.

It is obvious that the decrease in albumin and increase in globulin results in a gradual but constant reduction in the albumin-globulin ratio. A low A/G ratio is sometimes considered indicative of protein deficiency, but in pregnancy a very low ratio cannot be interpreted as indicative of a protein

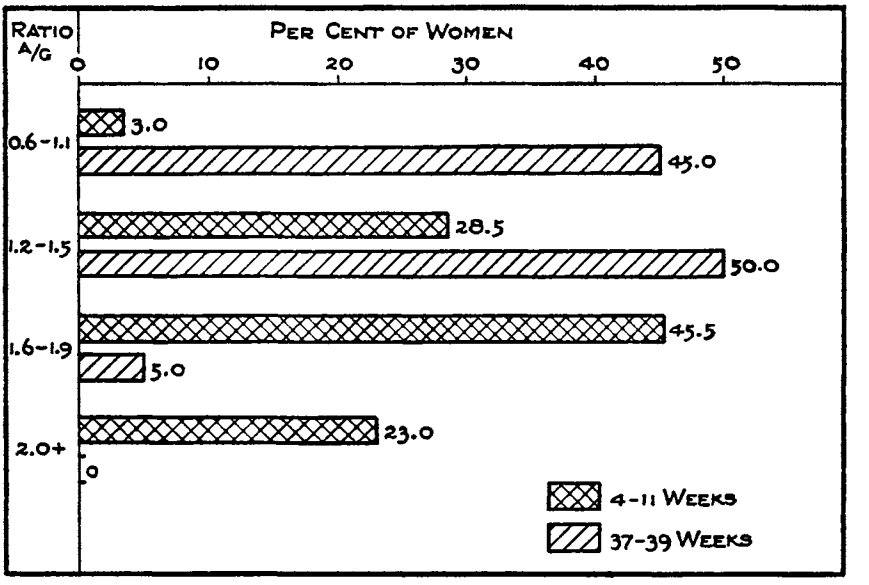


Fig. 6. Per cent of prenatal patients with the specified albumin-globulin ratio early in pregnancy and in the last three weeks.

deficiency. In the first trimester the A/G ratio averaged 1.7 and declined steadily to 1.2 in the last six weeks. This shift was characteristic of nearly all women. In Figure 6 the percentages of women for whom different A/G ratios were obtained on examination before the 12th week of gestation and in the last three weeks are shown. Early in pregnancy, 68 per cent of the cases had a ratio of 1.6 or higher, but at the end of pregnancy only 5 per cent had a ratio as high as 1.6. A low ratio late in pregnancy may be a favorable finding since it is associated with an accelerated production of globulin.

These average trends in blood values for all women give us a standard or level of reference against which to measure changes that may occur for women having various specific characteristics. One characteristic that differentiates the women and may be expected to affect the trends in blood levels as pregnancy progresses is their initial or early pregnancy blood levels.

In Figure 7 the change in hematocrit values and in hemoglobin is shown for three groups of women. The grouping was

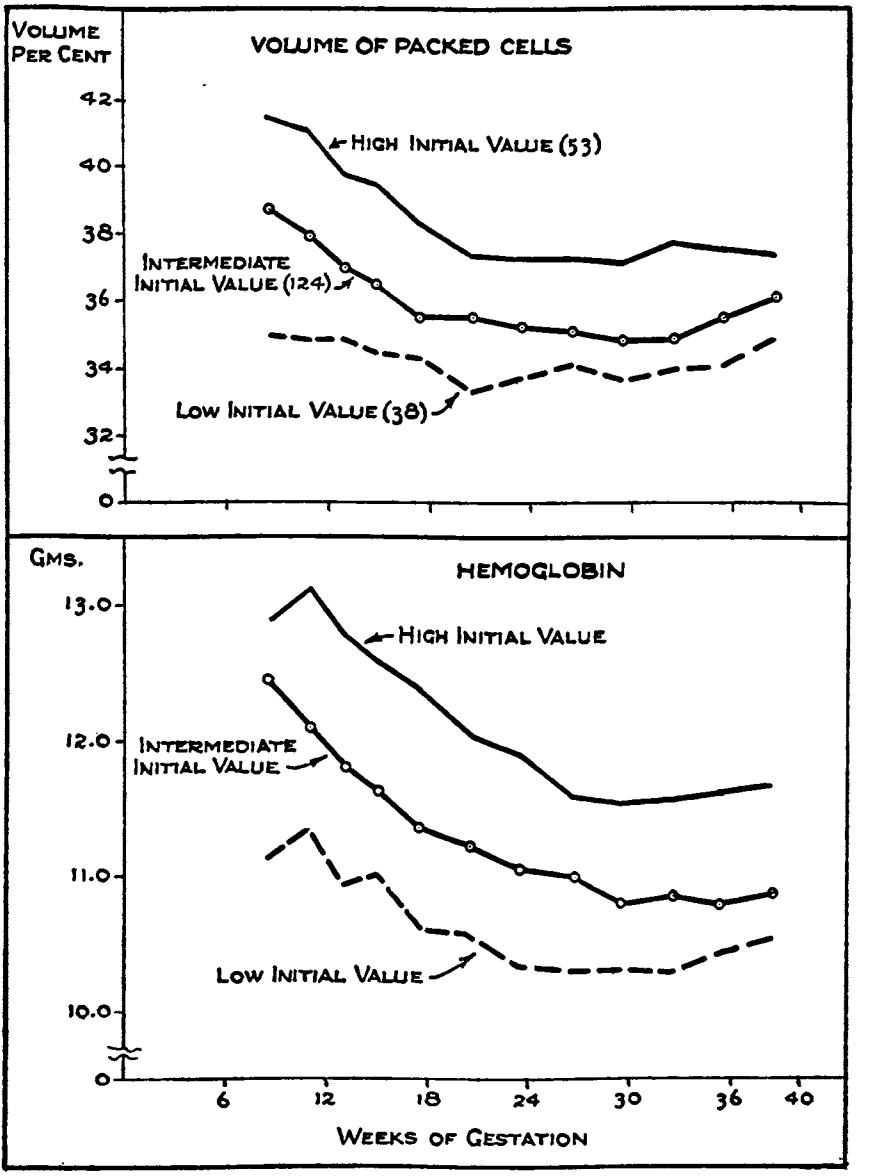


Fig. 7. Change in average hematocrit and in average hemoglobin values during pregnancy for three groups of women classified according to their hematocrit value at their first visit to the Nutrition Research Clinic, Pennsylvania Hospital.

made on the basis of the first hematocrit reading, and Group I includes those with relatively high volume of red cells, Group

II includes those with reading in approximately the middle 60 per cent of the distribution of readings at specific weeks of gestation, and Group III includes those with hematocrit readings below the lower limit of the middle 60 per cent.[8] In addition to the 161 white patients used for the total curve, 54 colored patients are included in averages for the three groups.

For the women with high and with average initial hematocrit values, the average curves throughout pregnancy for both the volume of packed red cells and for hemoglobin are quite similar and resemble the average curves for the total group which have been discussed. The group with low initial hematocrit values shows less decrease than the other two groups, especially for the volume of packed cells. The variation in the average volume of red cells during pregnancy for Group III is very slight; the minimum value is at about 20 weeks and is only 5 per cent less than the earliest value for the group, then the curve rises steadily after this point to a level about equal to the earliest value.

A similar comparison of three groups of women classified according to their initial total serum protein values is shown in Figure 8 for total protein, for serum albumin, and serum globulin. Again, the striking difference in these three groups is the small decrease in total serum protein during pregnancy for women with low initial levels compared with the decrease in the other two groups. The averages for serum albumin levels decrease for all three groups up to the last six weeks of pregnancy; but the drop in levels is greater the higher the initial level during the first half of pregnancy, and in the latter half there is no significant difference in the average albumin levels for the three groups, although the albumin level for the low group has some tendency to decrease more than the other

[8] Since the first visit to the prenatal clinic varied from the 6th to the 15th week of gestation, and the average hematocrit value decreased sharply during this period, hematocrit readings used as limits for the three groups were shifted for different periods of gestation. From distributions of hematocrit readings at less than 10 weeks, at 10–12 weeks, and at 13–15 weeks, upper and lower limits for the middle 60 per cent were obtained; and cases were classified as within, above, or below these limits. The average hemoglobin curves are for the women classified according to their hematocrit readings.

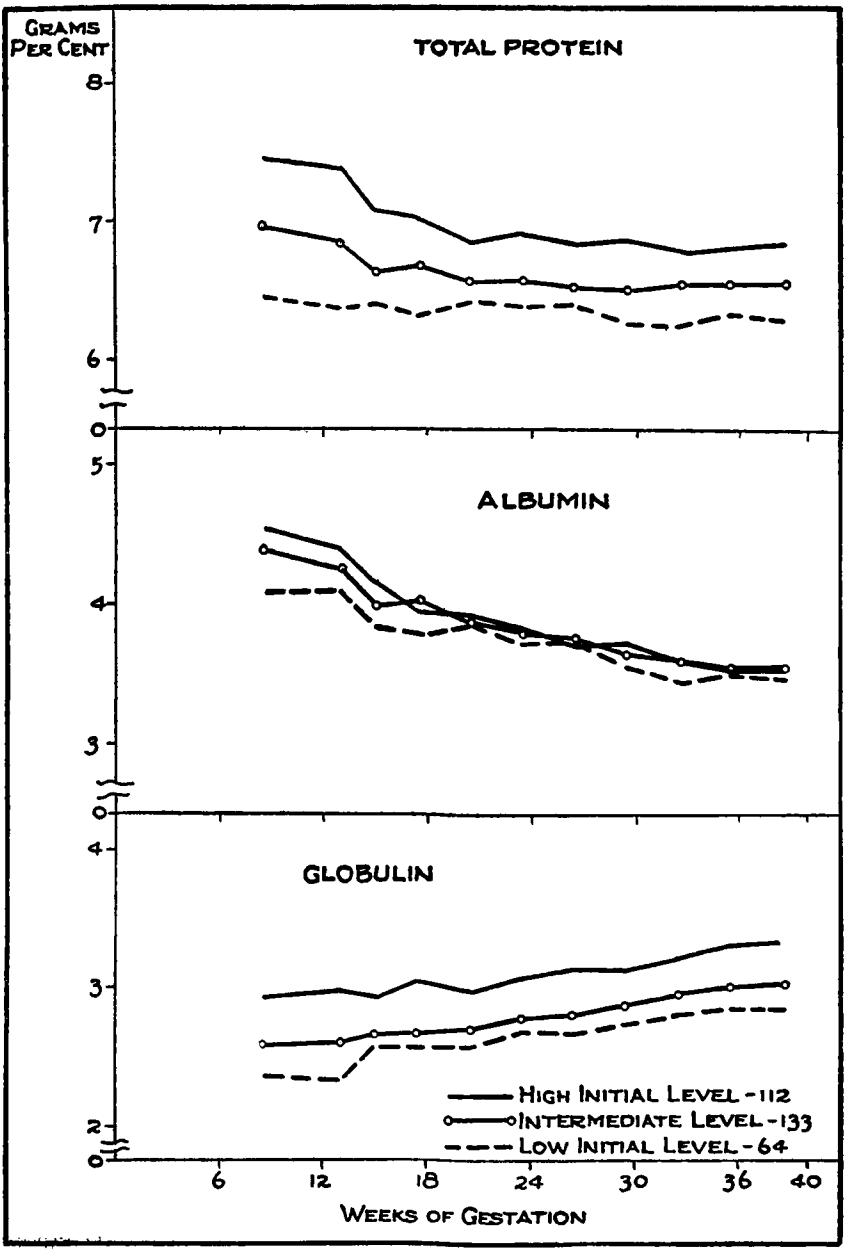


Fig. 8. Change in average total serum protein, in average albumin, and in average globulin during pregnancy for three groups of women classified according to their total serum protein value at first visit to the Nutrition Research Clinic, Pennsylvania Hospital.

groups in the early part of the third trimester. The maximum decrease in the average curves for albumin is 0.99 gm. for the high initial level group, is slightly less for the intermediate group (.83 gm.), and least for the low initial level group (.62 gm.), and the percentage decrease varies in the same order. All groups have an increase in serum globulin and it is the difference in globulin levels which maintains a difference in total serum protein levels for the groups throughout pregnancy. However, the increase in globulin varies inversely with the initial level of the groups and the maximum increases were .39 gm., .43 gm., and .50 gm., respectively. Thus, the increase in globulin for the low protein group was nearly equal to the decrease in albumin.

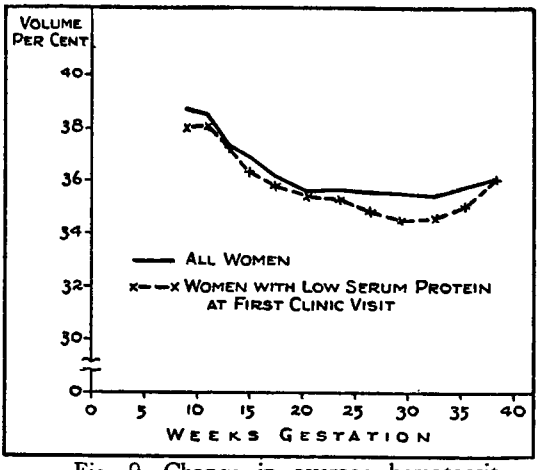


Fig. 9. Change in average hematocrit value during pregnancy for women having a low total serum protein at first observation compared with average change in hematocrit for all women.

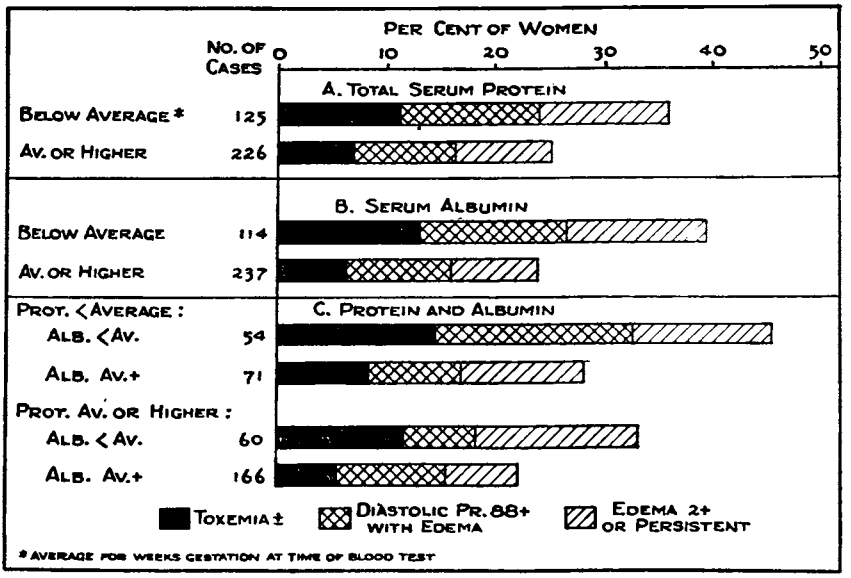
The question arises whether the smaller decrease in blood levels for women with low initial values is associated with a relatively small increase in plasma volume. No direct evidence is available, but some evidence on this point may be obtained from the change in hematocrit values for the women included in the group with low initial protein values. In Figure 9 the average hematocrit curve during pregnancy for the 64 women with low initial protein findings is compared with the hematocrit curve for the total group. The low protein group has slightly lower average volume of red cells but the decrease in hematocrit during pregnancy is also slightly greater than for the total group. Thus, there is no indication that these women did not experience an increase in plasma volume equally as large on the average as other women.

From the trends in red cell volume, in hemoglobin, and in serum protein and albumin shown by the curves for these different groups of women, it seems reasonable to conclude that a protective mechanism operates which tries to prevent these blood values from falling below some critical level. Under the stress of pregnancy there are apparently certain stimuli for the production of greater amounts of these blood constituents. In general, this is to be expected if the needs of pregnancy are to be met. But a relatively greater acceleration in the production of red cells and of protein by those women who began their pregnancy with blood values suggestive of a borderline deficiency indicates a remarkable response to some type of protective stimuli. The nature and significance of this response to the stress of pregnancy is not apparent.

Protein Levels and Symptoms of Toxemia

As a clinical problem, the important question is whether serum protein levels have any relation to complications of

Fig. 10. Frequency of symptoms associated with toxemia of pregnancy among 351 women classified: A, according to total serum protein level at first visit; B, according to serum albumin level at first visit; and C, according to protein level (as in A) subdivided by albumin level (as in B).



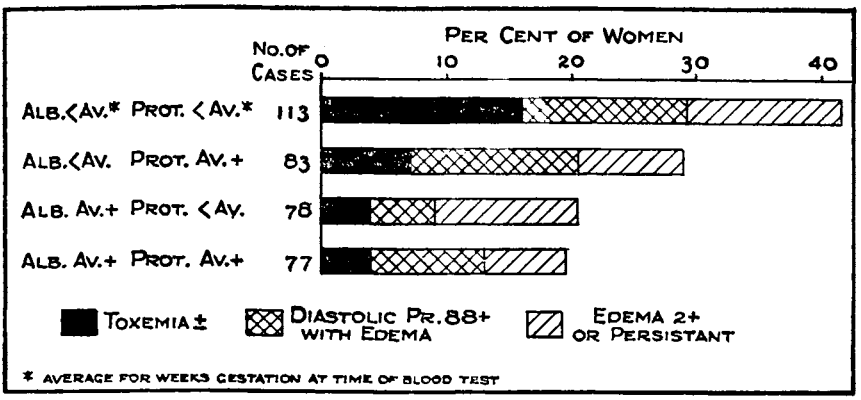


Fig. 11. Frequency of symptoms associated with toxemia of pregnancy among 351 women classified in four groups, two groups on basis of lowest serum albumin value relative to average level at a given period of pregnancy and each albumin group subdivided according to total serum protein value.

pregnancy. For 351 women supervised by the Nutrition Research Clinic,[9] the incidence of toxemia and of symptoms common to toxemia among women having different protein levels has been studied.

It is necessary to describe the symptoms and conditions which have been included in the incidence rates shown in Figures 10 and 11. There were only six cases diagnosed on the hospital charts as pre-eclampsia or eclampsia—too few for any statistical analysis. The prenatal histories of the 351 patients were reviewed and, on the basis of recorded symptoms, patients were classified in one of four categories as follows:

1. Toxemia, plus-minus:
    a. Pre-eclampsia or eclampsia.
    b. Hospitalized for control of excessive weight gain and/or other symptoms suggestive of potential toxemia.
    c. Blood pressure 140/90 one or more times with edema.
2. Elevated diastolic blood pressure (88 or higher) and edema at any time during pregnancy.

[9] These were all of the patients delivered up to September, 1949 for whom two or more total serum protein and albumin determinations were available, one of which was before 19 weeks of gestation, except for exclusion of the following: 3 cases of syphilis and 1 of gonorrhea; 2 cases of essential hypertension and 1 of chronic nephritis and hypertension; and 1 case of chronic pyelo-cystitis.

3. Edema rated ++ or worse or very persistent edema rated only +.
4. All other cases.

A total of 102 patients, 29 per cent of all cases, were classified in one of the three symptom categories.

The frequency of occurrence of each group of symptoms among women having different serum protein levels before 18 weeks of gestation is shown in Figure 10 and Table 1. The

Table 1. Incidence of symptoms associated with toxemia during pregnancy among women with average[1] and higher or below average serum protein and albumin levels early in pregnancy.

Classification of Women by Total Serum Protein and Albumin Levels at First Blood Examination (6–18 Weeks Gestation)	Number of Women	Per Cent of Women with Specified Condition[2]				
		Total	Toxemia + or −	Elevated Diastole (88+) and Edema	Edema 2+ or Persistent	Total of Three Symptom Groups
Total Women	441 351	100.0	8.5	10.5	10.0	29.0
A. Total Serum Protein:						
Below Average	138 125	100.0	11.2	12.8	12.0	36.0 29.0
Average or Higher	303 226	100.0	7.1	9.3	8.8	25.2 25.1
B. Serum Albumin:						
Below Average	127 114	100.0	13.2	12.3	14.0	39.5 33.9
Average or Higher	314 237	100.0	6.3	9.7	8.0	24.0 23.2
C. Protein and Albumin:						
Protein Below Average						
Albumin Below Average	58 54	100.0	14.8	18.5	13.0	46.3 34.5
Albumin Average +	80 71	100.0	8.5	8.5	11.3	28.2 25.0
Protein Average or Higher						
Albumin Below Average	69 60	100.0	11.7	6.7	15.0	33.3 33.3
Albumin Average +	234 166	100.0	5.4	10.2	6.6	22.3 22.6

[1] Average used for classifying an individual is always that for total serum protein and for albumin based on all determinations made at the same period of pregnancy as that at which the individual's first protein determinations were made.

[2] *See* text, page 253.

classification of women by protein levels was based on the *average* level for the specific week of gestation at which the protein determination for an individual had been made. Incidence rates are shown for the following groups of women:

1. Total serum protein:
    a. Women with protein level equal to or above average.
    b. Women with protein level below average.
2. Serum albumin:
    a. Women with albumin level equal to or above average.
    b. Women with albumin level below average.

A further subdivision of the women into four groups was made by subdividing each of the two total protein groups according to their serum albumin levels as in 2-a and 2-b above.[10]

The incidence rate (per cent of women affected) for each of the three symptom groups was higher for women with an initial total protein level below average than for those with an initial value equal to or above average. The differences for the separate groups of symptoms are not statistically significant, but the difference in rates for all symptoms combined is significant (P .01–.05).

When the incidence rates for women with different albumin levels, regardless of total protein, are compared, the rates for each group of symptoms are higher among women with below-average initial albumin levels. The difference for toxemia ± is larger than when total protein groups were compared and is statistically significant (P .01–.05). The differences for other separate symptom groups are not significant statistically, but the difference for all symptoms is significant ($P < .01$).

The incidence rates obtained when women are classified by both protein and albumin show greater differences, but the

[10] Classification by total serum protein and albumin is equivalent in the majority of cases to making a two-fold subdivision of the two albumin groups by globulin levels below average and equal to or above average. However, there are some exceptions which may be significant. For example, if the albumin level is much below average, the globulin level may be average or higher without bringing the total protein to the average level, and, also, if the albumin level is high, the total protein level may be above average although the globulin level is below average.

numbers of women in the separate protein-albumin groups are small and the pattern of difference is not constant for the three symptom classes. Toxemia ± occurred in 15 per cent of the women with below-average initial protein and below-average albumin as against a rate of 5 per cent in those with average or higher values for both protein and albumin. This difference is statistically significant (P .01–.05). Other differences for individual symptom groups are not significant. When all symptoms are combined there is a regular progression in frequency with the highest rate for those with low albumin and low total protein, the next highest for women with low albumin but average or higher total protein, and the lowest rate for women with average or higher albumin and average or higher total protein. The difference between the highest and lowest rate is very significant ($P < .001$).

From the previous discussion of the striking decrease in average albumin levels throughout pregnancy, even for women with relatively high initial levels, it is to be expected that some of the women who had average or better protein values early in pregnancy would have less than average values late in pregnancy. The incidence of symptoms associated with toxemia, therefore, was examined for women who maintained average or better levels and for those who failed to maintain average levels.[11] For this purpose, women were classified in one of the four protein-albumin groups on the basis of their lowest protein and albumin levels[12] relative to the average observed at any time in pregnancy.

The large number of women who failed to maintain average protein and albumin levels is shown by comparison of the numbers of women in the four protein-albumin groups in Table 2 and in Table 1. Thus, only 54 women (15 per cent of the total)

[11] Only one protein determination in the latter half of pregnancy was available for about 30 per cent of these women; therefore, the record of failure to maintain average levels was by no means complete.

[12] The few cases for which the lowest total protein level and lowest albumin level were not obtained at the same examination were classified according to the test with the lowest albumin rating. For exmaple, a case with less than average total protein—above average albumin at one test and above average protein—less than average albumin at another test would be put in the latter group.

had protein and albumin levels below average early in pregnancy, but 113 women (32 per cent) had these low levels at some time. Similarly, 166 women had total protein and albumin values equal to or higher than the average values at their first examination, but only 77 remained in this category throughout pregnancy.

Incidence rates for symptoms associated with toxemia are compared in Figure 11, for women classified into four groups on the basis of the lowest protein-albumin level observed at any time during pregnancy. The pattern of differences among the groups becomes more definite when the protein levels throughout pregnancy are considered.

The differences in frequency of cases of toxemia ± for the four groups are of special interest since these include the cases showing the most advanced symptoms. When albumin was

Table 2. Incidence of symptoms associated with toxemia of pregnancy among women classified according to lowest albumin level and total protein observed at any time during pregnancy.

Classification of Women by Lowest Albumin Level and Associated Total Protein During Pregnancy[2]	Number of Women	Per Cent of Women with Specified Condition[1]				
		Total	Toxemia + or −	Elevated Diastole (88+) and Edema	Edema 2 + or Persistent	Total of Three Symptom Groups
Total Women	351	100.0	8.5	10.5	10.0	29.0
Albumin Below Average:						
Protein Below Average	113	100.0	15.9	13.3	12.4	41.6
Protein Average or Higher	83	100.0	7.2	13.3	8.4	28.9
Albumin Average or Higher:						
Protein Below Average	78	100.0	3.8	5.1	11.5	20.5
Protein Average or Higher	77	100.0	3.9	9.1	6.5	19.5

[1] *See* text, page 253.

[2] Classification is made in relation to average albumin and average total serum protein values at specific weeks of gestation. Each woman had at least 2 protein determinations, one before 19 weeks of gestation and one after 23 weeks; 70 per cent of the women had 2 or more determinations after 23 weeks.

equal to or above average at every examination, the incidence of toxemia ± was the same (3.8 and 3.9 per cent) for the women with below-average protein and for those with higher total protein. This incidence is about one-fourth of the incidence among women with below-average albumin *and* below-average total protein. The difference is very significant statistically ($P < .01$). When albumin levels dropped below average but total protein remained at the average level or higher, the incidence of toxemia ± was less than one-half that for the women with low albumin and low protein. Although this difference is not statistically significant (P .05–.10), it strongly suggests a protective effect of a high globulin level when the albumin level falls.

Variation in rates for cases of elevated diastolic blood pressure with edema and for cases of marked edema alone was not as great among the different protein-albumin groups as that shown by toxemia. None of the differences among groups are statistically significant. There is a tendency for these symptoms to occur less frequently if the albumin level remained high.

In summary, it may be concluded that there was a very definite relationship between the albumin level during pregnancy and the occurrence of symptoms associated with toxemia. Among those women who maintained an average or higher albumin value, regardless of whether the total serum protein remained high, the incidence of these symptoms, especially the more advanced toxemia ±, was lower than among women with below-average albumin. Higher amounts of globulin (total serum protein) had no effect on the incidence rates when albumin was at a high level. However, if the albumin value dropped below the average level, the occurrence of symptoms was less frequent when the globulin level increased sufficiently to keep the total serum protein at the average or higher level than when the total protein also was below average. Furthermore, it may be noted that not only those women who had low albumin values early in pregnancy had a relatively high incidence of symptoms, but also those who initially had high values and

later dropped below average had a similar high incidence of symptoms. There were many cases of the latter type.

This relationship between serum protein and toxemia symptoms can not be interpreted as demonstrating a deficiency of protein intake as a factor in the incidence of symptoms, since factors other than intake may have affected the serum levels. One phase of the study now in progress at the Philadelphia Lying-In Hospital is to investigate the effect of an increased protein intake on serum protein levels and on the incidence of symptoms.

Individual changes in serum protein and in albumin during pregnancy show many variations from the average trends that have been presented. There are several patterns of change which are fairly characteristic of the changes observed for many of the women and which were associated with the symptoms that have been considered. It may be of interest to discuss several case histories which demonstrate some typical changes in protein and the associated symptom response.

First, there are the patients for whom changes in blood levels followed the general trend. In Figure 12, the record of case number 437 is of this type although the albumin level is below average throughout pregnancy. The albumin level decreases greatly from the 15th to the 21st week of gestation, it then stabilizes and declines only slightly at the middle of the third trimester. Total serum protein is above the average initially, decreases into the second trimester but remains at about the average protein level. During the second trimester, this patient had excess weight gain and a blood pressure of 130/88 at one visit. She was apparently in a marginal status but was classified as not having toxemia symptoms since the elevated blood pressure was not accompanied by a recognized edema.

Case 389, in Figure 12, is one of the group with relatively high albumin and high protein who developed a borderline toxemia and was sent into the hospital for control in the last week. Albumin levels declined at less than the average rate, and protein showed no decline until the 36th week when the

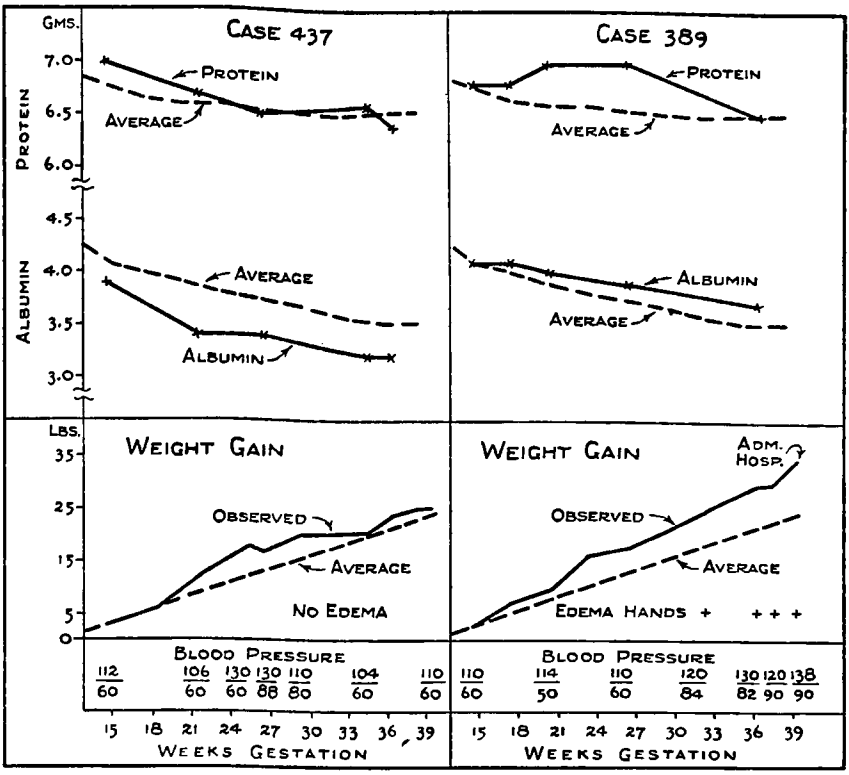


Fig. 12. Serum protein values, serum albumin values, weight gain, blood pressure, and edema observed during pregnancy for two individual patients.

value had dropped 0.5 gm. but was still average. There was no determination of serum protein between the 26th and 36th week, but two hematological readings were made and these showed a sharp decrease and it is very probable that protein also decreased early in the third trimester. A marked decrease in the middle of the third trimester is not uncommon and is often associated with appearance of some symptoms.

In Figure 13, two case histories are shown which are typical of changes in protein levels in many patients. A decrease occurs in the second trimester and is followed by some increase or no further decrease for several weeks, but a second drop occurs in the latter part of the third trimester. Thus there appear to be two periods of stress, at both of which some clinical signs may become evident.

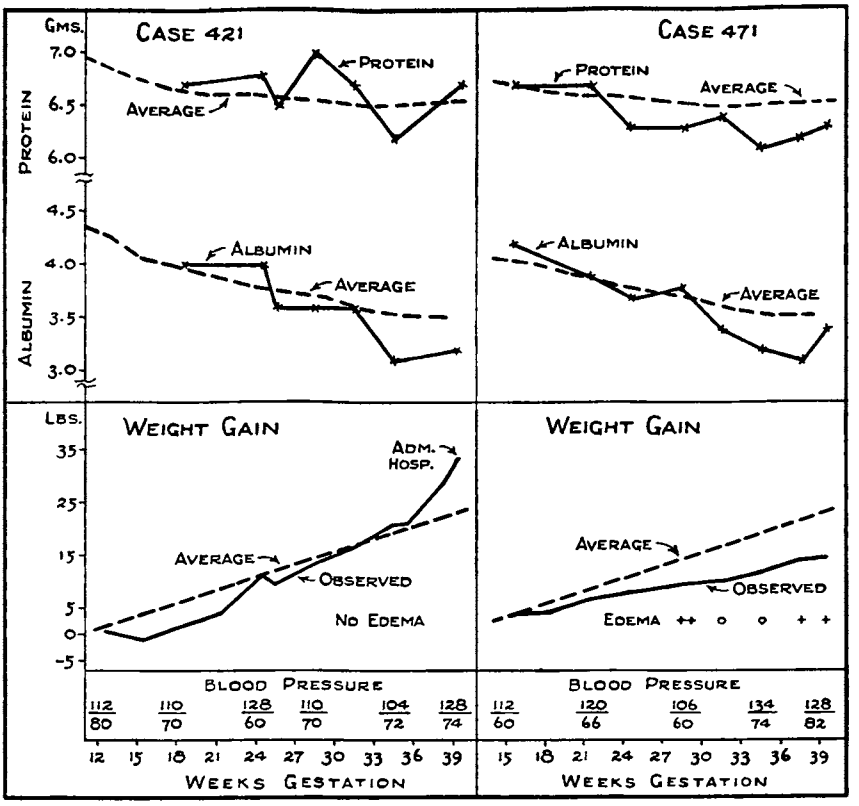


Fig. 13. Serum protein values, serum albumin values, weight gain, blood pressure, and edema observed during pregnancy for two individual patients.

Summary

Blood values for the volume of red blood cells (hematocrit), for hemoglobin, for total protein, and for albumin decreased markedly during the first half of pregnancy for a large group of women. The average decrease was approximately equal to that expected as a result of average increase in plasma volume. In the second half of pregnancy, although plasma volume continues to increase, both the hematological values and total protein and albumin values show only a slight further decrease. Globulin increased during the second and third trimesters. These data indicate a greatly increased production of these blood constituents.

The incidence of selected symptoms commonly associated

with toxemia of pregnancy was found to be much higher among women having both total serum protein levels and serum albumin levels below the average values for the group at any period of pregnancy than among women with either total protein or albumin values at the average or higher level. Incidence was lowest if the albumin value remained at the average or higher level, but a globulin value high enough to maintain the total serum protein at the average or higher level in spite of a low albumin level afforded considerable protection against occurrence of these symptoms.

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