HAEMODILUTION IN RHEUMATOID DISEASE

BY

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It has been suggested (Robinson, 1943; Dixon, Ramcharan, and Ropes, 1955) that the plasma volume in rheumatoid disease is greater than normal and that this increase may produce anaemia by dilution of the red cell mass. Such a mechanism might account for the refractory anaemia which sometimes occurs and in which there is a proportionate reduction of red cells and haemoglobin in the peripheral blood, the size and haemoglobin content of the individual red cell being essentially normal. Clearly, haemodilution does not explain the presence of hypochromic or microcytic red cells, nor the anaemia which responds to iron therapy; its possible role in the genesis of refractory anaemia, however, seemed to merit further investigation.

The blood, plasma, and cell volumes of groups of rheumatoid patients and of haematologically normal controls have therefore been estimated. As the blood volume is known to be influenced by sex, age, and bodily configuration, the controls were selected so that, in terms of these factors, the control and rheumatoid groups were as nearly alike as possible.

The results of the investigation do not indicate that haemodilution is a factor of importance in the genesis of anaemia in rheumatoid disease.

Material and Methods

(1) Patients Investigated.—The patients suffered from typical rheumatoid disease uncomplicated by blood loss or other conditions liable to affect haemopoiesis. So that surface area could be estimated from their height and weight, only ambulant patients, free from flexion deformities of the lower limbs and spine, were investigated. Volume estimations were made before any therapy, other than physiotherapy and simple analgesics, had been given. The controls were a mixture of healthy hospital workers and of patients who had locomotor disorders not likely to affect haemopoiesis, e.g. local osteo-arthritis, prolapsed disk, or psychogenic rheumatism; all had normal haemoglobin levels and sedimentation rates.

(2) Comparability of Groups.—There were 42 controls (20 male and 22 female) and 88 rheumatoid patients (35 male and 53 female). Their average weights, surface areas, and ages are shown in Table I, and their distributions by weight in Table II. The mean values and

<table>
<thead>
<tr>
<th>Table I</th>
<th>WEIGHT, SURFACE AREA, AND AGE. MEAN VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Group</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>Male</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid</td>
</tr>
<tr>
<td>Female</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table II</th>
<th>DISTRIBUTION BY WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodyweight (kg.)</td>
<td>40–49</td>
</tr>
<tr>
<td>Male</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid</td>
</tr>
<tr>
<td>Female</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid</td>
</tr>
</tbody>
</table>

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distributions of relevant groups agree quite closely, except for a difference of 3-5 kg. in the weights of the women, produced by an excess of "light-weights" in the rheumatoid group. Distributions by age and surface area are not shown, but were quite comparable; plotting the results of volume estimations against age revealed no material association in the range of ages studied here and the effects of age are therefore disregarded hereafter.

(3) Techniques.—Volume estimations were performed at about 12 noon, after the subjects had undergone a normal morning’s programme of work or physical treatment and had then rested for about 20 minutes. The technique employed was that of Gregersen (1944), in which a known volume of dye (Evans blue) is injected intravenously and the concentration of the dye in plasma withdrawn 10 minutes later is compared photometrically with a standard, consisting of a known dilution of the dye in the patient’s dye-free plasma. The examination of a single 10-minute specimen was considered adequate, as we have found that duplicate estimations by this technique regularly agree to within 5 per cent. Greater accuracy can be achieved by taking several specimens at intervals and retropolating the best fitting line through the observed optical densities to zero time. However, the mingling of the dye in the blood stream is complete in less than 10 minutes and its removal from the plasma proceeds at a slow and steady rate after injection. The rate of removal is slightly greater in rheumatoid disease than in health (Dixon and others, 1955), but the difference is not large enough to introduce an important error after 10 minutes; it would merely tend to produce a slight over-estimate of the rheumatoid plasma volumes. As this was an essentially comparative study, the examination of several specimens after injection was thought unnecessary.

Blood and cell volumes were calculated from the plasma volume and haematocrit. Haematocrits were estimated in duplicate, spun at 3,000 r.p.m. in a radius of 14.5 cm. until the cell volume became constant; readings were corrected for trapped plasma by the graph of Chaplin and Mollison (1952) and for the difference between whole body and venous haematocrits by the factor 0.91 of Chaplin, Mollison, and Vetter (1953). Heparin was the anticoagulant throughout, except for the Westergren erythrocyte sedimentation rate estimations, when 3-8 per cent. sodium citrate was used. Haemoglobin was measured by the cyanhaematin technique of King and Gilchrist (1947). The probability of differences between mean values being due to chance was computed from the "t" test for small samples.

Results

Mean values for plasma, cell, and blood volumes in relation to bodyweight and surface area are shown in Table III. In both sexes the rheumatoid patients had considerably lower cell volumes than the controls; the differences are statistically highly significant in relation to weight or surface area. The male rheumatoid patients had a higher mean plasma volume than the controls, the difference reaching statistical significance in relation to surface area. The plasma increase was, however, less than the cell decrease, so that the rheumatoid blood volume was lower than that of the controls, though the difference could quite easily have been fortuitous. In the rheumatoid women the plasma increase was almost the same as the cell decrease, so that their blood volume was the same as that of the controls; the difference in plasma volumes relative to bodyweight was significant.

The relationships between blood, plasma, and cell volumes and bodyweight in the women are displayed in Figs 1, 2, and 3 (opposite and overleaf). The

Table III

<table>
<thead>
<tr>
<th>Sex</th>
<th>Group</th>
<th>Bodyweight (ml./kg.)</th>
<th>Surface Area (l./sq. m.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volumes related to</td>
<td>Plasma</td>
<td>Cells</td>
</tr>
<tr>
<td>Male Control Mean</td>
<td>47.9</td>
<td>32.3</td>
<td>80.2</td>
</tr>
<tr>
<td>S.E.</td>
<td>1.8</td>
<td>1.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Rheumatoid Mean</td>
<td>51.1</td>
<td>24.7</td>
<td>75.8</td>
</tr>
<tr>
<td>S.E.</td>
<td>1.5</td>
<td>0.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Significance of difference</td>
<td>0.2</td>
<td>&lt;0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>Female Control Mean</td>
<td>48.7</td>
<td>26.2</td>
<td>74.9</td>
</tr>
<tr>
<td>S.E.</td>
<td>2.3</td>
<td>1.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Rheumatoid Mean</td>
<td>53.4</td>
<td>22.4</td>
<td>75.8</td>
</tr>
<tr>
<td>S.E.</td>
<td>1.4</td>
<td>0.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Significance of difference</td>
<td>0.05</td>
<td>&lt;0.01</td>
<td>—</td>
</tr>
<tr>
<td>Weighted Mean</td>
<td>51.2</td>
<td>21.8</td>
<td>73.0</td>
</tr>
<tr>
<td>Means corrected for Difference in Average Weight</td>
<td>50.9</td>
<td>21.6</td>
<td>72.5</td>
</tr>
</tbody>
</table>

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men, whose results are not illustrated, exhibited similar trends, which are summarized as regression equations in Table IV. The results are plotted as volumes per unit of weight against weight, as the associations are easier to see in this way.

Both the controls and the patients showed a tendency for the blood and plasma volume per unit bodyweight to decrease rather sharply as weight rose, the association being closest in the case of the plasma volumes of the rheumatoid women. If, for comparative purposes, it is assumed that there is a straight-line relationship between blood and plasma volumes and bodyweight, regression lines may be calculated, of the form \( y = a + bx \). The equations, given below Figs 1 and 2, show that there is no great difference between the regression coefficients of the control and rheumatoid groups. The standard errors of the differences between the regression coefficients of the groups are 0.20 and 0.27 for blood and plasma respectively; applying

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**Table IV**

Regression Equations of Blood, Plasma, and Cell Volumes (ml./kg.) of Men Upon Bodyweight (kg.)

<table>
<thead>
<tr>
<th>Volume</th>
<th>Group</th>
<th>Regression Equations</th>
<th>S.D. of Regression Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Control</td>
<td>Volume = 143.4 - 0.95 Wt.</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid</td>
<td>Volume = 113.9 - 0.59 Wt.</td>
<td>0.18</td>
</tr>
<tr>
<td>Plasma</td>
<td>Control</td>
<td>Volume = 82.5 - 0.52 Wt.</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid</td>
<td>Volume = 79.2 - 0.43 Wt.</td>
<td>0.13</td>
</tr>
<tr>
<td>Cells</td>
<td>Control</td>
<td>Volume = 60.0 - 0.42 Wt.</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid</td>
<td>Volume = 32.8 - 0.12 Wt.</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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Assuming straight-line relationships, the regression equations are as follows:

- **Control**, Volume (ml./kg.) = 122 - 0.81 \( x \) weight (kg.). S.D. of regression coefficient = 0.37.
- **Rheumatoid**, Volume (ml./kg.) = 130 - 0.99 \( x \) weight (kg.). S.D. of regression coefficient = 0.14.
Fig. 2.—Plasma volumes of women, plotted as in Fig. 1. An inverse relationship is again suggested.

Assuming straight-line relationships, the regression equations are as follows:

- **Control**, Volume (ml./kg.) = 85 - 0.62 x weight (kg.). S.D. of regression coefficient = 0.25.
- **Rheumatoid**, Volume (ml./kg.) = 97 - 0.80 x weight (kg.). S.D. of regression coefficient = 0.11.

Fig. 3.—Cell volumes of women, plotted as in Fig. 1. There is a slight inverse relationship between cell volume and body weight.

The regression equations are as follows:

- **Control**, Volume = 42.2 - 0.28 x Wt. S.D. of regression coefficient = 0.13.
- **Rheumatoid**, Volume = 34.4 - 0.22 x Wt. S.D. of regression coefficient = 0.17.

the "t" test, the values of p are found to be 0.7 and 0.5, indicating that the differences could readily be fortuitous. The relation between cell volume and weight was much less, though the trend was in the same direction. Because of these associations and of the excess of female rheumatoid subjects in the
weight group 40-49 kg, the mean values for the rheumatoid women have been recalculated after adjusting their weight distribution to that of the controls. The resultant weighted means are shown in the penultimate row of Table III; the pattern of changes is similar to that found in the male patients, namely, a marked reduction in cell volume with a smaller increase in plasma and somewhat reduced blood volume.

The relationships between volumes and circulating haemoglobin level are shown in Figs 4, 5, and 6. Blood and plasma show no important relationship to haemoglobin level, but cell volume is directly and quite closely related, and the results from the rheumatoid subjects merge into those of the controls. If a straight-line relationship is assumed and regression lines are calculated, the difference between the regression coefficients of the control and rheumatoid groups is 1.50, and the standard error of the difference is 1.23; the difference could readily be fortuitous (0.3 > P > 0.2).

It seemed possible that the complicating effects of bodyweight might have obscured relationships between blood or plasma volume and haemoglobin level, and that the slightness of the relationship between cell volume and weight was due to varying degrees of anaemia. Accordingly, results were recalculated after constructing regression lines for blood plasma volumes upon weight, and for cell volume upon haemoglobin level, assuming that
straight-line relationships obtained. Individual results were then expressed as differences from the expected values. Plotting these differences against the corresponding haemoglobin levels revealed no closer association than before, but plotting the cell volumes as differences from the values expected from the degree of anaemia did slightly increase the closeness of the association between cell volume and bodyweight.

There was no relationship between plasma volume and disease activity as judged by the erythrocyte sedimentation rate (Fig. 7); blood and cell volumes were similarly unrelated.

To exhibit possible differences in volume between anaemic and non-anaemic rheumatoid patients, avoiding the complicating effect of bodyweight, a separate group of non-anaemic female patients whose weights lay between 50 and 60 kg. was examined. In Table V the results are contrasted with those from the anaemic patients of the same weight range. The groups have virtually identical blood volumes, the anaemic group showing a reduction in cells equal to the increase in plasma.

The volumes observed in the last six men and seven women with rheumatoid disease whose anaemia proved refractory to parenteral iron therapy are shown in Fig. 8 (opposite). The outlines and mean values for the whole groups are inserted for comparison. The figures for men for all volumes were generally lower than those for the whole group; the women’s results were scattered at random within the group boundaries and their mean values were slightly higher than the mean of the whole group, in proportion to the difference in average bodyweight. Neither Fig. 8 nor Table V gave any indication of the dilution of a normal volume of cells by an increased volume of plasma.

**Discussion**

The Evans blue method of estimation of plasma volume has been criticized, but it gives results which agree with those obtained by methods employing human serum albumin tagged with radio-iodine (Schultz, Hammarsten, Heller, and Ebert, 1953; Inkley, Brooks, and Krieger, 1955) and seems therefore to offer a reasonable estimate. Values for cell and whole blood volumes obtained from the observed plasma volume and haematocrit are perhaps less accurate, because the haematocrit is influenced by the centrifugal force applied and some plasma is inevitably trapped in the red cell column. Further, the haematocrit value of blood obtained from large veins is higher than that of the circulation as a whole. However, for comparative purposes, using standard conditions of centrifuging

**Table V**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Cases</th>
<th>Mean Age (yrs)</th>
<th>Mean Bodyweight (kg.)</th>
<th>Mean Surface Area (sq. m.)</th>
<th>Hb. Value (g./100 ml.)</th>
<th>Volume related to</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemic Non-</td>
<td>14</td>
<td>47</td>
<td>55.0</td>
<td>1.56</td>
<td>10.6</td>
<td>Mean S.E.</td>
</tr>
<tr>
<td>anaemic</td>
<td>18</td>
<td>48</td>
<td>54.5</td>
<td>1.54</td>
<td>13.2</td>
<td>Mean S.E.</td>
</tr>
<tr>
<td>Significance of Difference</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

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**Fig. 7.—Plasma volumes of rheumatoid women (ml./kg.) plotted against erythrocyte sedimentation rates (mm./hr). No relationship.**
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Fig. 8.—Blood, plasma, and cell volumes of six men and seven women with rheumatoid disease and anaemia refractory to parenteral iron, plotted against weight. Results shown as solid circles and mean value as a solid square. Boundaries of whole groups of rheumatoid subjects shown as open circles connected by interrupted lines. Whole group mean value shown by a cross.

Dixon and others (1955) compared simultaneous estimates of the blood volumes of normal and rheumatoid subjects by the Evans blue and $^{51}$Cr-tagged red cell methods. In ten haematologically normal women, the mean value for blood volume by the dye method was 13 per cent. higher than by the tagged cell technique. It is notable that this figure of 13 per cent. was the same as that obtained by Barnes, Loutit, and Reeve (1948a), who compared estimates of blood volume obtained by the dye method and by the Ashby differential agglutination technique. Barnes, Loutit, and Reeve (1948b) did not consider that the higher figures given by the Evans blue method were explained by loss of dye from the blood stream or by any of the other obvious sources of error. It is conceivable that the dye method does, in fact, measure a slightly larger fluid compartment, plasma being able to penetrate relatively further, for example, into the interstices of sinusoids than red cells.

From the standpoint of the present investigation, the important fact is that the relation between the results from dye and tagged cell methods is the same in normal and rheumatoid subjects (Dixon and others, 1955), and comparison of our controls and rheumatoid patients by the dye method is therefore justifiable.

For any comparison of blood, plasma, or cell volumes, it is essential to refer to some measurement of bodily size, weight and surface area being the standards usually employed. Gibson and Evans (1937) analysed the relations between these volumes and bodyweight, surface area, and other factors in healthy people. They found that the blood volume tended to be higher the greater the weight, though there were wide individual variations. The relationship was not a simple "straight-line" one, for, above a moderate weight, increase in total blood volume failed to keep pace with increasing weight, so that the volume per unit weight fell. This disparity between increasing weight and blood volume was much more marked in women.

Because of these weight effects, our controls and patients were matched as nearly as possible in weight distribution. The matching was satisfactory in the men, but there was an excess of "light-weights" in
the group of rheumatoid women, the mean weights of the female groups differing by 3·5 kg. Figs 1 and 2 show that the observation of Gibson and Evans (1937), that volume per unit weight decreases as weight rises, is applicable to our subjects and that this weight effect is of considerable magnitude. If, for comparative purposes, it is assumed that a straight-line relationship obtains between blood or plasma volume per unit weight and bodyweight, regression lines may be calculated for the various groups. For both blood and plasma, the slope of the lines in the control and rheumatoid groups is quite similar and the differences could readily be fortuitous. Thus, the data, although inadequate to demonstrate that the regression lines for rheumatoid subjects and controls are the same, are perfectly consistent with this possibility. It seems very likely, therefore, that the associations of blood and plasma volumes with bodyweight in the rheumatoid patients are simply the manifestations of a general relationship.

If the results from controls and patients are combined, common regression lines may be calculated and used to determine how much of the difference between the average volumes of the control and rheumatoid groups is due to the inequality of their average weights. It emerges that the lower weight of the rheumatoid group would cause their average volumes of blood and plasma to be 3·3 and 2·5 ml./kg. higher than those of the control group. After allowing for this weight effect in the women (Table III, last row), the volume changes in male and female rheumatoid patients exhibit a common pattern, in relation both to weight and to surface area; compared with the controls, they show a marked reduction in cell volume and a smaller increase in plasma, so that the whole blood volume is somewhat reduced.

The other factor which might affect the results of volume estimations in rheumatoid disease is the presence of anaemia. The mean haemoglobin levels of our male and female rheumatoid subjects were 3·8 and 2·6 g./100 ml. below those of the controls. The volume changes in several different types of anaemia were investigated by Gibson, Harris, and Swigert (1939). These authors found a consistent pattern of changes in all the types studied, namely a reduction in red cell mass, proportional to the degree of anaemia, an increase in plasma volume, of lesser degree than the red cell reduction, and a slightly or moderately reduced blood volume.

This pattern of changes is precisely the one observed in our patients after correction for the effects of bodyweight. We conclude, therefore, that the volume changes in our patients are adequately explained by the operation of two factors of general importance, namely the effects of bodyweight and of the presence of anaemia. The slightly higher average plasma volume of the rheumatoid patients can be readily explained by their lower weight and haemoglobin levels, and there is no need to postulate a primary inflation of plasma volume.

The possibility exists that an increase of plasma occurs in patients who have very active disease or iron-refractory anaemia. Fig. 7, in which plasma volume is shown to be unrelated to the erythrocyte sedimentation rate (mm./hr. Westergren) lends no support to the first possibility. Table V, which compares groups of anaemic and non-anaemic patients of the same weight range, and Fig. 8, which displays the blood, plasma, and cell volumes of thirteen iron-refractory anaemic patients, give no evidence of dilution of a normal volume of cells by a raised plasma volume, either generally in anaemic subjects or in those refractory to iron.

It remains to consider the discrepancy between the present findings and those of Dixon and others (1955), who observed a significant increase in plasma but no significant decrease in cell volume in ten female rheumatoid patients as compared with ten controls. These authors found that the mean plasma volume of their patients was 12-8 ml./kg. higher than that of the controls, the difference in average weight being 11·7 kg.; they corrected for the weight difference by a statistical method depending on the slope of the regression line of volume upon weight. From a small number of observations, with inevitable biological variations, however, the slope of a regression line can only be determined within fairly wide limits, and our observations suggest that differences in weight have a larger effect than the slope of Dixon’s line expresses. Calculation from our regression equations shows that a difference in bodyweight of 11·3 kg. would produce differences of 11·7, 8·5, and 3·2 ml./kg. in blood, plasma, and cell volumes respectively; if these corrections are used to compare rheumatoid and control groups of “equal” weight, Dixon’s rheumatoid patients exhibit plasma and blood volumes which are 4·3 and 1·6 ml./kg. higher than those of the controls and a cell volume which is 2·7 ml./kg. lower. The excess of plasma over the amount needed to replace the diminished volume of cells is thus 1·6 ml./kg.; this excess might well have disappeared had further data been collected.

Summary

The blood, plasma, and cell volumes of groups of rheumatoid patients and controls have been com-
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The groups were matched as nearly as possible in terms of weight, surface area, and age.

Blood and plasma volumes were considerably affected by bodyweight, and differing weights accounted for some of the volume differences between control and rheumatoid subjects.

When the effects of weight were eliminated, the rheumatoid subjects, whose average haemoglobin level was below normal, exhibited volume changes common to many types of anaemia, namely, considerable reduction in red cell volume with a smaller increase in plasma volume, and, in consequence, some reduction in blood volume.

Patients with very active rheumatoid disease or iron-refractory anaemia did not exhibit particularly high plasma volumes.

It is concluded that the increase in plasma volume observed in rheumatoid disease is adequately explained by the operation of two general factors which influence the blood, plasma, and cell volumes, namely bodyweight and the presence of anaemia. The hypothesis of primary hydremia, causing haemodilution, appears to be unnecessary.

My thanks are due to Drs. G. D. Kersley, J. B. Bennett, L. C. Hill, and P. W. McKeag for permission to study patients under their care. I am grateful to Dr. G. Herdan for statistical guidance and helpful criticism.

REFERENCES


L'hémodilution dans la maladie rhumatismale
Résumé

A l'aide de l'hématocrite et de la méthode de Bleu d'Evans on a comparé le volume globulaire, du plasma et du sang total chez des rhumatisants et des témoins.

Les groupes furent autant que possible assortis aux points de vue poids, surface corporelle et âge.

Les volumes du sang et du plasma furent considérablement influencés par le poids du corps et les variations pondérales furent la cause de quelques unes des différences portant sur les chiffres du volume, entre les rhumatisants et les témoins.

En ne tenant aucun compte de l'influence du poids, les rhumatisants, dont le chiffre moyen d'hémoglobine était au-dessous de la normale, accusèrent des altérations de volume communes à des nombreux types d'anaémie, c'est-à-dire une considérable diminution du volume globulaire accompagnée d'une plus petite augmentation du volume plasmatique et, en conséquence, d'une réduction du volume sanguin total.

Les malades atteints d'une maladie rhumatismale très active ou d'anaémie réfractaire au fer n' accusèrent pas de volumes plasmatiques particulièrement élevés.

On en conclut que l'augmentation du volume plasmatique observé dans la maladie rhumatismale est convenablement expliquée par l'influence de deux facteurs généraux qui agissent sur les volumes sanguin, plasmatique et globulaire: le poids du corps et l'anaémie. L'hypothèse d'hydremie primaire causant l'hémodilution n'apparaît pas nécessaire.

La hemodilución en la enfermedad reumática
Sumario

Con la ayuda del hematocrito y del método de Azul de Evans se compararon el volumen globular, plasmático y sanguíneo en sujetos y en algunos testigos.

Ambos grupos fueron ajustados, cuanto posible, desde el punto de vista de peso, superficie del cuerpo y edad.

Los volúmenes sanguíneo y plasmático fueron considerablemente afectados por el peso del cuerpo y las variaciones ponderales fueron la causa de algunas de las diferencias respecto a las cifras del volumen, entre los reumáticos y los testigos.

Sin tener cuenta el peso, los reumáticos con cifras de hemoglobina debajo de lo normal presentaron alteraciones de volumen comunes a numerosos tipos de anemia, quiere decir una diminución considerable del volumen globular con pequeña aumenación del volumen plasmatico y, consecuentemente, de una reducción del volumen sanguíneo.

Los casos de enfermedad reumática muy activa o de anemia refractaria al hierro no presentaron volúmenes plasmáticos particularmente altos.

Se concluye que la incrementación del volumen plasmático observada en la enfermedad reumática se explica adecuadamente por la influencia de dos factores generales que actúan sobre los volúmenes sanguíneo, plasmático y globular: el peso del cuerpo y la anemia. La hipótesis de hidremia primaria causando la hemodilución no parece necesaria.
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