A STUDY OF THE ERYTHROCYTES IN CONGESTIVE HEART FAILURE, AND THEIR RELATION TO BLOOD VISCOSITY,

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I N T R O D U C T I O N

Heart failure may be described as a condition in which, with lessening of the muscular power of the heart, an efficient circulation cannot be maintained, so that the tissues fail to receive a sufficient amount of oxygen, and to be adequately relieved of their waste products of metabolism, such as carbon dioxide.

The congestive type of heart failure is present when, with failure of the right side of the heart, associated with diminution in velocity of the blood flow, stasis occurs in the pulmonary and systemic circulations. The conspicuous clinical symptom of congestive cardiac failure is dyspnoea, which, as Lewis (78) explains, becomes more distressing even at rest, with increase in the venous congestion, the latter being recognised by such signs as engorgement of veins, cyanosis, hepatic enlargement, scanty, high-coloured urine, dropsy, and the signs of congested and oedematous lungs.

While the red blood corpuscles, which function as transporters of oxygen, and are also to some extent concerned with the carriage of carbon dioxide, have been studied fairly extensively in heart failure with venous congestion, it is noticeable from the literature that much more attention has generally been directed to variations occurring in their number, than to possible changes occurring in individual red cells, as for example in their size.

For the purpose of this thesis, therefore, besides giving a general résumé of the literature, I have carried out an investigation into the volume and diameter of the erythrocytes in congestive heart failure, as well as studying, at the same time, their number and haemoglobin content, so that a more complete picture of possible changes occurring in red cells in this condition might be presented.

As the erythrocytes also play an important part in the viscosity of the blood, variations in which are known to occur in cardiac failure (as indicated in the survey of the literature), it was considered of interest to relate the study of the size and number of the red cells to a study of the blood viscosity, which was accordingly undertaken.

Congestive heart failure was in the majority of cases in this investigation secondary to chronic valvular disease, as for example, mitral stenosis, or aortic regurgitation with secondary mitral regurgitation, but it has also been secondary to other conditions, such as chronic bronchitis and emphysema, adherent pericardium, arterio-sclerosis, and chronic nephritis.

The plan of the investigation was to study a series of normal subjects in order to obtain standard figures for comparison, for the technique employed, and with the same technique, to study a series of cases of well-compensated heart disease, and a series of cases of congestive heart failure. It was considered of interest to add the compensated cases, so that the results in cardiac failure might be compared with those obtained in cases

where the equilibrium of the circulation was still maintained.

In many of the heart failure cases, observations were also made when improvement in clinical condition occurred, and in four of the cases, a more detailed study was made, with frequent determinations, to show the effect of exacerbations and remissions of the circulatory symptoms. The effects of oxygen administration, venesection, and diuresis have also been studied.

As failure of the circulation may be considered to occur temporarily in severe exercise in normal persons (McDowall (86)), it was considered of interest, in addition to studying cases of cardiac failure, to study normal subjects under such conditions, and this was done in three subjects.

The work was carried out at the Liverpool Heart Hospital, from the wards of which the cases of congestive heart failure were obtained. The normal subjects comprised members of the medical and nursing staffs of the hospital, students, and persons obtained from private sources. The cases of compensated heart disease were obtained from the hospital Out-patient Department, and from private sources.

All the blood examinations, for the estimation of volume and diameter of erythrocytes, erythrocyte count, haemoglobin percentage, and viscosity of the blood, have been carried out by myself.

M O R P H O L O G Y

A brief description of the morphology of the red cell seems appropriate. It is generally described as a biconcave circular disc, with a semi-permeable membrane, and consisting of two substances, stroma and haemoglobin, together with a certain amount of water and salts, and also a certain amount of lecithin and cholesterin.

Cooke (24), in his recent description of the human erythrocyte, doubts the presence of a histological cell membrane, but states that on the surface of the cell, a condensation of lipin molecules occurs, which acts as a cell envelope, and probably has some physico-chemical relationship with the protein of the stroma. The cell membrane has certain characteristic properties of permeability, in which it is believed that the lecithin and cholesterin, besides maintaining the integrity of the corpuscles, play an important part (72).

The gas exchange function of the red cell depends on the presence of the haemoglobin. Mathews (92) states that while the latter was generally assumed to be in solution in the corpuscle, recent observers have shown that it is probably a constituent of the membrane, being distributed on its surface.

The red blood corpuscles are elastic and flexible, and change their form and volume easily under different conditions. They have certain osmotic relationships with the plasma, becoming shrivelled with concentration of the latter, and swollen with water,

when the plasma becomes diluted.

Changes in size of the erythrocytes depend on two essentially different factors - physico-chemical, and biotic (Capps (22)). The physico-chemical factors relate chiefly to the process of osmosis, while the biotic factors are concerned with the growth and development of the cell, which Capps describes as the anabiotic factor, and with cell degeneration, which he calls the katabiotic factor.

The average number of red cells present in health is usually given as 5,000,000 per cubic millimetre for males, and 4,500,000 per c.mm. for females, although Dyke (39) in a recent criticism of generally accepted normal values, states that according to recent observers, the average red cell count for white males is nearer 5,500,000 per c.mm. of blood. Gulland and Goodall (56), however, are of the opinion that most counts over 5,000,000, when not due to some obvious cause, are generally to be accounted for by some slight congestion, or other circulatory disturbance.

The average diameter of the red cell is normally about 7.5μ. Bell, Thomas, and Means (11) state that the majority of observations on red cell diameter for both wet and dry preparations lie between 7.5μ and 8.0μ. They obtained normal averages of 7.6μ for males, and 7.7μ for females, there thus being no significant difference between the sexes.

The normal average measurements given by a few other writers are shown below :-

Writer	Ref. No.	Average Diameter in μ
Cabot	18	7.5
Da Costa	27	7.5
Capps	22	7.65
Price-Jones	112	7.4
Howell	73	7.7
Gulland and Goodall	57	7.5
Poulton	111	7.5
Grosh and Stifel	55	7.42
McCormick	85	7.32
McDowall	87	7.5

Price-Jones (113) has shown that diurnal variations in the size of normal red cells occur in association with body activity, presumably due to alteration in blood reaction. These observations have been confirmed by Pijper (108). Bell, Thomas, and Means (11) state that the mean diameter of red cells is dependent on blood reaction, a shift to the acid side causing an increase in diameter, and a shift to the alkaline side, causing a decrease. Price-Jones (113) has also shown that violent exercise causes a greater increase in red cell diameter than that occurring with ordinary bodily activity, which was confirmed by Wiechmann and Schürmeyer (129), and by Bell, Thomas, and Means (11). Ponder and Saslow (110)

however, who obtained results which were at variance with those of Price-Jones, and Wiechmann and Schürmeyer, doubt the presence of a diurnal variation, or an increase after exercise.

HISTORICAL

A. An attempt is made to give a brief and general résumé of the literature appertaining to the number, size and haemoglobin content of red blood cells, and their relation to blood viscosity, in chronic heart disease, with special reference to congestive heart failure. It will be noted that in comparison with the attention which has been directed towards variations in the number of erythrocytes in cardiac failure, very little work has apparently been done on the subject of possible changes occurring in their volume and diameter.

Cabot (19) (1898) related the blood picture in heart disease to three stages :-

1. Stage of full compensation, in which no changes occur.

2. Stage of acute failure of compensation, with lowering of blood pressure, in which dilution of the blood occurs (more marked in venous than in capillary blood), and the red cell count and haemoglobin percentage are lowered.

3. Stage of chronic cyanosis with passive congestion of internal organs and peripheral circulation, in which the blood shows concentration (more marked in the capillary blood), with a raised erythrocyte count and haemoglobin percentage. This is considered by Cabot an apparent polycythaemia, which he states is generally present in any condition involving general circulatory stasis and cyanosis from cardiac insufficiency.

In his "Clinical Haematology", Da Costa (28) (1902) states

that in well-compensated, valvular heart lesions, the blood shows no deviations from normal, as such lesions are of themselves unable to produce blood changes. With failure of compensation, however, a hydraemia or dilution of the blood mass occurs, with lowering of red cell count and haemoglobin percentage, which, with the establishment of stasis and cyanosis, gives way to concentration of the blood mass, with high haemoglobin values and polycythaemia. The latter, which he states may be sufficient to mask a co-existing anaemia, and is commonly in the neighbourhood of 6,000,000 red cells per c.mm., is mainly due to the passage of fluid from plasma to tissues, and perhaps to loss of water through the lungs. Da Costa is inclined to deprecate the tendency to associate certain blood conditions with definite valvular lesions, as, for example, with mitral or aortic disease, and states that the general disturbances dependent on the lesion, and not the lesion per se, account for alterations of the normal blood picture observed in heart disease.

The views of earlier observers on the state of the blood in heart disease with special reference to heart failure, are well summarized by Ewing (45) (1901), as follows :-

1. In advanced endocarditis, with failing compensation, there is a tendency to concentration of the blood, associated with the establishment of venous stasis, under which circumstances the blood tends to lose water, and become richer in red cells, more so in the capillaries than in the veins.

2. This polycythaemia is the combined result of stasis, dyspnoea and cyanosis, transudation of blood serum, and possibly also of other obscure factors which lead to polycythaemia at high altitudes.

3. A condition of relative hydraemia sometimes occurs, associated with a fall in red cell count.

4. The tendency to anaemia is usually masked by the peculiar condition of the circulation.

5. Regarding individual lesions, mitral disease is usually associated with polycythaemia, while aortic disease is usually found with less concentrated blood, although variations from this rule are known to occur.

An early observation on the possibility of changes in size of the red cells in cardiac disease was that made by Vaquez (124) in 1895, which, although referring to congenital heart disease, and therefore not actually to cardiac failure, is nevertheless considered of sufficient importance to be mentioned, - at least for the purposes of comparison - as anoxaemia and cyanosis, to which he relates his findings, are both features of congestive heart failure. Vaquez found that besides a progressive increase in the number of erythrocytes in cardiac cases attended by chronic cyanosis, there also occurred an increase in their individual size. He writes: "L'augmentation du nombre des globules rouges, n'est pas la seule modification importante que l'on constate dans le sang des malades atteints de cyanose chronique. J'ai en effet remarqué que chez ces mêmes sujets, les hématies présentaient assez habituellement une

augmentation de volume, également progressive et pouvant atteindre de fortes proportions."

He found that the increase in size of the individual red cells in such cases was associated with a corresponding increase in the haemoglobin content of the cells and to quote his own words concluded that "... chez les cyanotiques, le globule rouge est, à la longue, chargé d'une quantité plus considérable d'hémoglobine, en même temps que son volume s'accroît."

Vaquez regards the increase in number and size of the red corpuscles in these cases as a defensive reaction against the tendency to deficient oxygenation of blood from disturbance of respiratory function. In other words, as expressed by him (125) in "Diseases of the Heart", the increase in size of red corpuscles in chronic cyanosis has the same object as the increase in number, namely, to compensate for the anoxaemia, and increase the respiratory capacity of the blood.

It is interesting to note, however, that although the increase in size of the erythrocytes was regarded as being due to the same cause as the increase in number, it apparently did not occur at the same time as the latter, for Vaquez (124) found that it was usually not manifested until some time after the polycythaemia had developed.

Another early reference to the size of red cells is the observation of Eiger (40) in 1909, in cases of emphysema with cardiac dilatation, where he found that besides an increase in the number of red cells from peripheral stasis, there also occurred an increase in the volume of cells in proportion to

plasma, which in many cases was associated with increase in volume of the individual red cells.

In his contribution to "A System of Medicine", Drysdale (37) (1905), considered that the rise in red cell count occurring in cyanosis accompanying general venous engorgement, as in valvular heart disease with failure of compensation, was probably due to alteration in the circulation, whereby the red cells accumulated to some extent in the peripheral vessels.

Buchanan (16) (1909) states that in well-compensated cases of valvular heart disease, there is no blood change, but that with failure of compensation, there may at first be a "serous plethora" and a fall in haemoglobin and erythrocytes in the peripheral blood, and that when stasis is established the peripheral blood may show polycythaemia with increased viscosity.

In his review on polycythaemia, erythrocytosis and erythraemia, Parkes Weber (128) (1908) considers that blood-stasis (impeded circulation) affecting a large portion of the body may probably sometimes give rise to a secondary (general) absolute polycythaemia, as well as more directly to a (local) relative polycythaemia, and that generally speaking, the red blood cells are increased in imperfect oxygenation of the blood and tissues in circulatory disturbances due to chronic heart conditions. Parkes Weber upholds the view that the increase in number of red cells is a compensatory reaction for deficient oxygenation of the tissues, as at autopsies on

cases of chronic cyanosis of cardiac disease (and also of pulmonary disease), he noted that, although the red colour of the bone-marrow of the shafts of long bones was due partly to engorgement with blood, evidence of abnormal haematopoietic activity was also present. Parkes Weber further states that the increase in viscosity present with increased number of red cells, is demonstrated in the blood from patients with polycythaemia and cyanosis of cardiac or pulmonary origin, in whom the viscosity of the blood was raised.

In his review on the viscosity of the blood, Allbutt (2) (1911), states that in diseases of the heart, excess of CO_2 raises the viscosity and renders the blood stream sluggish. Access of oxygen, however, lessens the viscidity of the blood, thereby easing the heart, and forwarding the blood stream. Allbutt quotes Von Korányi, who found that inhalation of oxygen was followed by a reduction in the number of red cells, which helped to reduce the viscosity.

Coming to the more recent literature on the subject under investigation, (where more attention is also given to the number of red cells than to individual cells, apparently little work having been done on the size of erythrocytes in heart failure) Sahli (120) (1918) states, that the blood picture in chronic venous stasis may simulate polycythaemia, owing to retention of corpuscles in the capillaries from the slow current. On the other hand, polycythaemia may actually result, since certain organs, in consequence of this "sifting"

of corpuscles, contain too little haemoglobin, and therefore more active blood formation results, due to functional adaptation of the bone marrow.

In "Diseases of the Heart and Aorta", Hirschfelder (69) (1918) states that while in compensated heart disease, the blood viscosity is unchanged, in venous stasis, associated with polycythaemia, it rises considerably, and in the hydraemia often associated with anasarca and "broken compensation", the viscosity is diminished.

Emerson (41) (1921) writes that while cardiac compensation is good, the blood is normal, but with hydraemia of the blood, the red counts are low, and with chronic stasis and cyanosis, the count rises, and may conceal an anaemia.

In the course of an investigation on the size of red blood cells in emphysema, Price-Jones (114) (1922) estimated red cell diameters (without corresponding volume indices) in 15 cases of congestive heart failure. While he found the average of the mean red cell diameter values for the emphysema cases to be higher than that for the healthy subjects, the average of the mean red cell diameters for the heart failure cases was, contrary to his expectations, not significantly different from the normal average. There was, however, a slightly greater variation in the red cell diameter values for the heart failure cases than for the healthy subjects, although not to the same extent as for the emphysema cases.

In the 15 cases of cardiac failure studied by Price-Jones,

the individual lesions have not been noted, nor were the results related to the clinical conditions of the patients at the time of making the observations. As both these factors should probably be taken into consideration in a study of the size of red blood cells in congestive heart failure, it is considered by the writer that definite conclusions cannot be drawn from Price-Jones's series of results, except that it is possible for the size of the erythrocytes in heart failure with dyspnoea, cyanosis, and venous congestion, to show no deviation from the normal. In any case, Price-Jones's investigation is really in connection with emphysema, with which his conclusions are chiefly concerned.

In "Diseases of the Heart", Cowan and Ritchie (26) (1922) state that the cyanosis of heart disease is usually accompanied by polycythaemia which Gibson (quoted by Cowan and Ritchie (26)) suggested was a compensatory change, due to the lessened activity of the red cells as oxygen carriers.

An erythrocytosis, or absolute increase in red blood cells, which is compensatory in nature, is also stated by Monro (99) (1925), in "A Manual of Medicine", to occur in cases of cyanosis, the latter being frequently the result of deficient oxygenation of the blood.

Anders and Boston (4) (1925) state that when a haematological study is made in tricuspid regurgitation, when effusion into serous sacs has occurred, and oedema of the subcutaneous tissues, and cyanosis of the extremities, are present, the number of red cells per c.mm. of blood often exceeds that of

the normal. They quote cases of cyanosis that they have seen, in which the red cells numbered from 5,000,000 to 8,000,000 per c.mm., with a haemoglobin percentage of from 90 to 100, and state that this increase in red cells and haemoglobin results from the blood condensation following the extravasation of its liquid elements into the tissue spaces and serous cavities.

In valvular heart disease with good compensation, the viscosity of the blood, according to Gulland and Goodall (58) (1925) remains unchanged. In heart failure without oedema it tends to be increased, more so with the presence of polycythaemia, and in heart failure with oedema, it is generally decreased. The same writers further state that the number of red corpuscles is not usually raised in fully compensated heart disease, or in aortic regurgitation with failure of compensation, but that it is usually above normal in mitral disease when compensation has failed, and in many conditions of chronic strain and dilatation (e.g. emphysema, chronic bronchitis) without valvular disease, in which compensation is inadequate.

That an erythrocytosis, or absolute increase in red cells, occurs with failing circulation and imperfect oxygenation of the tissues, is stated to be the case by Fitz (46) in the "Oxford Medicine", and Abbott (1) (1927), in Osler and McCrae's "Modern Medicine", both writers stating that this increase in erythrocytes is associated with an increase in blood volume.

In describing physiological erythrocytosis, such as occurs

at high altitudes from deficiency of oxygen, Piney (109) writes :- "Such physiological erythrocytosis has pathological counterparts: for example, the poor aeration of the blood in chronic morbus cordis is accompanied by an increase in the number of red corpuscles." Piney describes this as a symptomatic polycythaemia.

A similar secondary polycythaemia, or erythrocytosis, which is an effort on the part of the haematopoietic system to compensate for defective oxygenation of the blood, is stated by Thursfield (123) to be observed in the cyanosis of failing circulation.

French (51) considers that such a secondary polycythaemia is an attempt on the part of nature to compensate for the failing circulation, by distributing the haemoglobin over a larger corpuscular area.

In his review on polycythaemia, Harrop (64) (1928), states that although polycythaemia often accompanies heart disease, where it rarely exceeds 7 million red cells, and occurs more often in mitral disease than in aortic disease, and in cases where emphysema exists, or secondary changes occur in the lungs, it has nevertheless been observed that many cases of severe heart disease with secondary lung changes, show no increase in blood count whatever.

In describing the increase in the richness of corpuscles in congenital heart disease, where the number per c.mm. may reach 7,000,000 or more, Muir (100) (1929), in his "Textbook of

Pathology" states that a similar change, though less in degree, may be observed in chronic venous congestion in cardiac cases, e.g., in mitral stenosis. Muir states that this increase in red cells is to be regarded as a compensatory one, resulting probably from the fact that a diminished amount of blood passes through the lungs in unit of time.

In a study of haemoglobin percentage and red cell count in Bright's disease, myocardial failure, and hypertension, Ashe (7) (1929), included cases of congestive cardiac failure occurring in patients (i) with chronic nephritis; (ii) without nephritis; and (iii) with hypertension. The cases of cardiac decompensation not associated with nephritis of any type, were used as control cases. Ashe found that in all three types of heart failure, the red cell count was relatively high compared with the haemoglobin percentage, so that the colour index in congestive heart failure was characteristically low.

B. A brief survey of the literature regarding variations in red cell count, haemoglobin percentage, and size of individual red cells after violent exercise, is conveniently given here.

Violent exercise appears to be generally associated with increase in red blood cell count and haemoglobin percentage. This increase has been put down to various causes, which are chiefly: (i) concentration of the blood; (ii) liberation of additional corpuscles from the capillaries; and (iii) splenic contraction.

Concentration of the blood caused by increased perspiration after severe muscular work was considered by Boothby and Berry (15) (1915) to be the cause of the increase in red cells and

haemoglobin, and in this connection Anders and Boston (5) refer to a "physiological polycythaemia" following physical exercise with profuse perspiration.

Hawk (66) (1903), Dautrebande and Davies (29) and Peters, Bulger, Eisenman and Lee (107) all considered that the increase in red cells or haemoglobin percentage obtained after short vigorous exercise, was associated with the liberation of additional blood cells from stagnant capillaries, from the increased blood flow and vascular dilatation which the exercise produced.

Dorothy Dufton (38) obtained an increase of red cells after exposure to carbonic acid, and made the suggestion that any factor, such as violent exercise, which produces a temporary rise in the concentration of carbonic acid in the blood, will produce a corresponding formation of fresh corpuscles.

In the exercise experiments of Scheunert and Krzywanek (quoted by Barcroft and Poole (9)), where increase in erythrocyte count and total corpuscular volume occurred, Barcroft and Poole (9) considered that contraction of the spleen was an important mechanism in giving an increment of corpuscles, although it may not have been responsible for the whole phenomenon.

It appears also that increases in red blood corpuscles after exercise can take place very quickly, and often be fairly considerable. Wadi (quoted by Arnold and Krzywanek (6)) found rapid and often considerable increases in red cells in young people on exertion under conditions of sport.

He records one case where he noticed an increase of

erythrocytes by 800,000 in one cubic millimetre of blood. It is interesting to note that Arnold and Krzywanek (6) found the increase in number of red cells after bodily exertion to be generally more marked in blood from a larger vein than in blood from capillary regions, although of the capillary areas, the blood from the finger tip showed an increase in red cells which more nearly approached that observed in the venous blood.

Regarding the size of red cells, Price-Jones (113), as previously mentioned, found a definite increase to occur in the sizes of red cells (as shown by increase in their mean diameter values) after short violent exercise. Increase in diameter was also obtained by Wiechmann and Schürmeyer (129) with overcharges of carbonic acid in the blood after bodily exertion. This increase in red cell diameter after exercise has, however, been doubted by Ponder and Saslow (110).

METHODS

(a) Size of Red Cells.

In this part of the work, both the volume of the individual erythrocyte, relative to the normal (as expressed by the volume index), and its diameter value in microns, have been estimated, the former by the haematocrit method, and the latter by the projection method suggested by Price-Jones (113).

I. The haematocrit volume index.

The haematocrit is an instrument which records the corpuscular volume percentage of the blood, and consists of a haematocrit head attached to a centrifuge machine. The haematocrit head is a metal frame, holding two fine capillary tubes, graduated in hundredths, which are filled with blood, and centrifugalised until the corpuscles are sedimented.

The earlier observations with the haematocrit were concerned chiefly with the volume of the packed cells, and Capps (22) placed the subject on a more practical basis, by suggesting the term "volume index" as indicating the average volume of the individual red cell.

The volume index is the ratio of the haematocrit reading expressed as a percentage of the normal, to the red cell count expressed as a percentage of the normal. Thus, as described by Rossdale (116), where the haematocrit reading is 50.0, which is the normal reading, and said to be 100 per cent., and where the red cell count is 5,000,000 per c.mm., which is a normal count,

which is said to be 100 per cent.,

$$\text{the volume index} = \frac{\text{haematocrit per cent.}}{\text{red cell count per cent.}} = \frac{100}{100} = 1$$

Rossdale states that it may be concluded that the normal limits of the volume index lie between 0.90 and 1.00. Capps (22) obtained an average reading for volume index of 0.99, in his series of 10 normal subjects, the range of variation being from 0.96 to 1.05.

Regarding the blood to be used with the haematocrit, Capps is of the opinion that the best results are obtained by the use of blood, without added anti-coagulant. This is confirmed by Rossdale (116), who besides using capillary whole blood, also used citrated and oxalated capillary blood, and citrated venous blood, with definite proportions of blood and citrate solution, and found that the capillary whole blood method gave the most accurate readings, both in normal and diseased states. The other methods gave definitely lower readings, so that Rossdale discarded them in favour of the capillary whole blood method, which, when employed, gave a normal average haematocrit reading of 50.

With regard to the reliability of haematocrit readings, Rowntree and Brown (117) in their study of the volume of blood and plasma, state that although haematocrit readings have recently been questioned as to reliability, their experience with 350 cases, and more than 1000 determinations of blood volume, leads them to consider that haematocrit readings are reliable for all practical purposes.

Campbell (20) found by experiment that the haematocrit method was valid as a means of measuring relative size of corpuscles differing as a result of osmotic change, in spite of the fact that it was considered that the cells were subjected to too much pressure by rotating in the centrifuge, so that no true estimate of their size could be obtained. In reply to such criticism, however, Campbell states that if the conditions observed in each case are the same, so that compression during rotation tends to cause a similar degree of change in each experiment, a comparison between the size of corpuscles in various conditions may still be made, even if the absolute size is somewhat modified.

In this investigation fine capillary tubes were used (this being an essential point in the estimation of red cell volume, as separation is slow and incomplete if a wide tube is used (35)), and the haematocrit head was provided with a screw adjustment to hold the tubes in position, and prevent blood from escaping. The capillary tubes were cleaned with 1 per cent. acetic acid, followed by distilled water and absolute alcohol, and then dried with ether. Capillary blood without added anti-coagulant was used, and two tubes filled in each case, as a control of the results. Great care was taken to prevent coagulation by scrupulous cleanliness and speed in operation, the blood being placed on the centrifuge within a few seconds after withdrawal, for which purpose the centrifuge was set up near the ward.

The haematocrit was used on a water-motor centrifuge, acting

under water pressure. When the centrifuge was rotated as rapidly as possible, the speed, recorded by a cyclometer type of revolution counter, was found to be 3,000 revolutions per minute. In order to find the time of duration of centrifugalisation to sediment normal blood completely with this centrifuge, a series of six preliminary observations were made on the writer's blood, and it was found that a constant reading for total cell volume was obtained after centrifugalising for 30 minutes at a speed of 3,000 revolutions per minute. In each case, centrifugalisation was allowed to continue up to 40 minutes, and frequent readings taken, but it was found that a constant reading was obtained after 30 minutes, after which no alteration in reading occurred. Normal whole blood was thus completely sedimented with this centrifuge in 30 minutes, at a speed of 3,000 revolutions per minute, and by using the same centrifuge a uniform technique - consisting of the above speed and time of duration of centrifugalisation - was employed throughout this investigation for the estimation of total red cell volume. It may be mentioned that the technique that I have used corresponds to that employed by Rowntree and Brown (117) who also rotated their centrifuge for 30 minutes at a speed of 3,000 revolutions per minute.

In the preliminary observations above mentioned, an average haematocrit reading of 50 was obtained, with a corresponding average red cell count of 5,045,000.

The readings are shown below :-

Haematocrit Values:

50, 50, 51, 48, 51, 50.

(average 50)

Red Cell Counts:

5,008,000; 5,040,000; 5,072,000;

4,992,000; 5,056,000; 5,104,000.

(average 5,045,000)

The maximum deviation from the mean in the above haematocrit readings was 4 per cent., and the average reading of 50 corresponds to that obtained by Rossdale (116), and to the generally accepted normal reading.

II. Red Cell Diameters.

The projection method of Price-Jones (113) has been used in this work for determination of red cell diameters, with a slight modification in the method of measurement.

Blood was obtained by pricking the finger, and films made in the ordinary way. These were dried in the air, without heat, and stained in Jenner's stain for two minutes, and afterwards in an aqueous solution of eosin (5 per cent.) for two minutes, to intensify the stain.

By placing a strong lamp behind a microscope, a convenient form of projection apparatus was arranged, so that the image of the microscopic field was projected on to a sheet of paper, fixed to the wall. A thin portion of the film was chosen, where the cells were well separated, and 200 red cells were

then outlined in pencil. Care was taken to take only rounded cells, any showing crenation being discarded. The field was moved after every 5 to 10 cells, in order to obtain as great a variation as possible, and after outlining 200 cells, the blood-slide was removed, and a slight modification made in the method by projecting the counting-slide of a Thoma-Zeiss haemocytometer on to the same field, and ruling in a few large counting squares.

The maximum diameter and the minimum diameter of each red cell were measured as accurately as possible with a millimetre scale, and the average obtained, and after finding the average for the 200 cells the estimation of the actual red cell diameter was then arrived at by comparison with a side of the counting square. This is best illustrated by an example :-

Suppose the average of the maximum and minimum diameters of the 200 red cells was found to be 10.5 mm., and the length of each side of the haemocytometer square on the same field to be 7 cm. (70 mm.);

The counting square actually measures $\frac{1}{400}$ sq. mm., so that each side is $\frac{1}{20}$ mm., hence on the microscopic field 70 mm. corresponds to $\frac{1}{20}$ mm. in actual measurement. The calculation is then made as follows :-

70 mm. corresponds to $\frac{1}{20}$ mm.

$\therefore$ 10.5 mm. " " $\frac{1}{20} \times \frac{10.5}{70}$ mm.

$= \frac{10.5}{1400}$ mm.

$= 0.0075$ mm.

or 7.5 microns, or μ

Therefore the average or mean red cell diameter value for this particular blood would be taken as 7.5 μ.

In this particular case, the microscope had evidently been set for a magnification of 1,400 diameters, which would therefore be the magnification if the microscope was set every time in the same position, and at the same distance from the wall. However, the counting-slide was projected on to the microscopic field in every case to obtain accuracy as far as possible.

Despite the errors introduced into this method by changes taking place in blood cells during the drying and staining of films, Price-Jones (113) has shown that although the diameters in dried films were smaller than those in moist preparations, nevertheless the changes in the one preparation were parallel to those in the other. He recommends the dry film method as the best for routine use.

As to the number of red cells measured, Price-Jones (113) considers that a number between 200 and 500 gives reasonable accuracy, and for the sake of convenience, has worked out arbitrary standards of differences based on statistics, by means of which it can be said, according to the number of cells measured, whether a difference between two means is real and significant, or probably, but not conclusively, real. These standards of differences are expressed in absolute values, and based on the principle of 5 times the probable error of the difference between two means, which Price-Jones considered

would allow for such errors as those due to differences in the making, and rate of drying, of the films, errors of measurement, and so forth, which were not sufficiently covered by the ordinary 3-times rule. For 200 cells (which is the number measured in this work) Price-Jones states that a difference between two means of 0.32 μ, would be regarded as real and significant.

In this investigation, therefore, a difference between two average red cell diameters of 0.32 μ or more, has been regarded as being real and significant. On the other hand, differences between 0.25 μ and 0.32 μ have been regarded as probably, although not conclusively, real, while differences below 0.25 μ have generally been disregarded.

(b) Red Cell Counts.

These were made with the Thoma-Zeiss haemocytometer, an average of two readings being taken in each case.

(c) Haemoglobin.

The haemoglobin determinations were made by a Haldane's haemoglobinometer, shown by Meakins and Davies (93) to be accurate within about 1 per cent., if sufficient care be taken.

The colour index was estimated in the usual way.

(d) Viscosity of the Blood.

Viscosity estimations were not commenced until at a slightly later stage of the investigation, but the method employed is conveniently described here.

A uniform technique was again used, all the viscosity

determinations being made with the Hess viscosimeter, which provides a simple and accurate method for the clinical determination of blood viscosity, utilizing only a small quantity of blood. The principle underlying this instrument is based on Poiseuille's law, which states that fluids under equal temperature and pressure passing through capillary tubes of equal radius, vary in their rate of flow in direct proportion to their viscosities. Capillary blood was used, without added anti-coagulant, the latter being found to be unnecessary, as after a little experience with the instrument, a viscosity determination could be made very quickly, providing the capillary tubes were kept perfectly clean. This was done by never leaving the blood in contact with the capillary tube longer than necessary, expelling it directly after completing a determination, and rinsing the tube with ammonia.

The actual viscosity estimations were made by comparison with distilled water, the viscosity of which equals 1.0. The writer from time to time tested the viscosimeter by using distilled water instead of blood, and if there was any deviation from 1.0 in the viscosity of the water, the tubes were thoroughly cleansed, and the test repeated, until there was no discrepancy.

Regarding temperature, the Hess viscosimeter carries a thermometer by which the temperature can be noted. According to Dr. Hess - as stated in the instructions for use of the instrument - the best temperature for the determinations

should be from 17° C. to 20° C., the possible variations occurring within this range being negligible, for clinical purposes. In this investigation the viscosity estimations were carried out at a practically constant temperature of 17° C.

In view of diurnal variations in the haemoglobin content of the blood, as observed by Dreyer, Bazett and Pierce (36), and also by Rabinovitch (115), and of possible diurnal variations in the size of the red cells, as previously indicated, the blood specimens in this work were taken at about the same time in the afternoon.

RESULTS

Normal Subjects.

A series of 12 normal subjects were studied, and the results are shown in Table I.

The following averages were obtained :-

Haematocrit reading 50.08; red cell count 5,039,000; haemoglobin 96 per cent.; volume index 0.99; mean diameter value 7.48 μ ; colour index 0.95.

Normal Subjects after Violent Exercise.

As previously stated, 3 normal subjects were studied after short, violent exercise. The form of exercise employed was standing-running, as rapidly as possible, to exhaustion. All three subjects were healthy young males, two of whom (Dr. S.S. and W.R.J.) were studied for Table I. By an interesting coincidence, the former - namely, Dr. Scheinfein, to whom I express my thanks for acting as a subject for the experiment - had been used as a healthy subject by Long[1] in a study of lactic acid in the blood of normal resting males.

The results before and immediately after exercise, are given in Table II, and in the case of Dr. S., and W.R.J., the exercise experiment was performed just after the blood had been examined for Table I. In order to facilitate quickness of work immediately after the exercise, I was assisted in the taking of blood specimens in these experiments by the House Physician, Dr. Irene Papenfus, to whom my thanks are also due.

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[1] Long, C.N.H., Journ. Physiol., Camb., 1924, LVIII, 455.

TABLE I

NORMAL SUBJECTS

Initials	Sex	Age	Red Cells per c.mm.	Haemo-globin %	Haema-tocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ
Dr. S. S.	M	31	5,320,000	102	52	0.97	0.95	7.50
Sister L. F.	F	30	5,040,000	98	50	0.99	0.97	7.58
A.M. (writer)	M	31	5,020,000	98	50	0.99	0.97	7.60
Nurse V. C.	F	26	4,968,000	92	48	0.96	0.92	7.32
Nurse M. G.	F	18	4,720,000	88	48	1.01	0.93	7.40
Nurse M. J.	F	27	5,136,000	97	51	0.99	0.94	7.47
W. R. J.	M	18	4,852,000	92	49	1.01	0.94	7.34
Dr. G. McL.	M	29	5,160,000	98	50	0.97	0.95	7.43
Dr. I. P.	F	29	5,016,000	96	51	1.01	0.95	7.54
P. M.	F	23	4,984,000	94	50	1.00	0.94	7.50
E. E.	M	36	5,200,000	100	53	1.02	0.96	7.60
T. D.	M	25	5,056,000	98	50	0.98	0.96	7.50
Average			5,039,000	96	50.08	0.99	0.95	7.48

TABLE II

EFFECT OF SHORT VIOLENT EXERCISE TO EXHAUSTION IN 3 NORMAL SUBJECTS

Subject		Red Cells per c.mm.	Haemo-globin %	Haema-tocrit Reading	Volume Index	Colour Index	Mean Diam. in μ
Dr. S. (age 31)	Before exercise	5,320,000	102	52	0.97	0.95	7.50
	After exercise	5,860,000	114	64	1.09	0.97	7.94
W. R. J. (age 18)	Before exercise	4,852,000	92	49	1.01	0.94	7.34
	After exercise	5,380,000	102	58	1.08	0.94	7.71
E. P. (age 25)	Before exercise	4,912,000	94	49	0.99	0.95	7.48
	After exercise	5,324,000	100	59	1.10	0.94	7.90

It will be seen that in the 3 cases, there has occurred, after violent exercise, an increase in red cell count, haemoglobin percentage, and total red cell volume. These increases were apparently of rapid occurrence, and in the case of Dr. S., and W.R.J., the counts were increased by over 500,000 red cells per c.mm., and the haemoglobin values by 12 and 10 per cent. respectively.

The volume and diameter of the individual red cells were also increased after violent exercise. According to the standard of differences, all three subjects showed real and significant increases in average red cell diameters after exercise, namely 0.44 μ in Dr. S., 0.37 μ in W.R.J., and 0.42 μ in E.P. The corresponding increases in volume index were approximately 12 per cent., 7 per cent., and 11 per cent., respectively.

No material change was noted in the colour index.

Normal Viscosity.

Although viscosity determinations in this work were not commenced until after the first 12 cases of congestive heart failure shown in Table VI were studied, it seems appropriate, when dealing with normal subjects, to state the normal viscosity results, at this stage. The technique has already been described.

Hess (68) put the range of normal viscosity in males from 4.0 to 5.5, with an average of 4.74, and in females from 4.0 to 5.4, with an average of 4.4. He considered that viscosity values of below 4.3 and above 5.3 as abnormal in males, and below 3.9 and above 4.9 as abnormal in females.

The normal range of viscosity according to a few other observers is as follows :-

Hirsch and Beck (70) from 4.50 to 5.89.

Bence (12) from 4.37 to 6.80.

Determann (34) from 4.05 to 5.54.

Table III gives the viscosity values obtained by the writer in 10 normal subjects, most of whom were again members of the hospital staff, together with a few students.

T A B L E III

VISCOSITY READINGS IN NORMAL SUBJECTS

Sex	Viscosity (Water = 1.0)
M	5.5
F	5.0
M	5.6
M	5.4
F	4.8
M	5.3
F	5.3
F	5.4
M	5.9
F	5.0
Average	5.32

The average viscosity for the two sexes was 5.32. This is in fairly close agreement with the average normal viscosity values of 5.45 and 5.30 for males and females respectively, which Harris and McLoughlin (61) obtained with the same viscosimeter, in their recent study of the viscosity of the blood in high blood pressure, carried out at the Liverpool Heart Hospital. They considered any viscosity above 6 or below 4, whether for male or female, as being abnormal, and this criterion of difference has been adopted in the present investigation.

Compensated Heart Disease.

A series of 20 cases of fully compensated heart disease (the majority of which had chronic valvular lesions), have been studied. They are divided into two groups, the first comprising 12 cases with results shown in Table IV, studied before viscosity determinations were commenced, and the second, comprising a further series of 8 cases, with results in Table V., in which viscosity estimations are included.

From a comparison of the average results for the 20 cases comprising Tables IV and V, with those for the healthy subjects in Table I, it was found that :-

(a) The average volume and diameter of the individual red cells in the compensated heart cases, showed no deviation from the average volume and diameter of the red cells of the healthy subjects.

(b) The average red cell count of the compensated cases was almost similar to that of the normal subjects, although a few individual cases (mostly of aortic regurgitation)

TABLE IV

CASES WITH COMPENSATED CARDIAC LESIONS

Case	Sex	Age	Lesion	Red Cells per c.mm.	Haemo-globin %	Haema-tocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ
1	F	35	Aortic Regurgitation	4,696,000	84	47	1.00	0.89	7.48
2	M	18	Mitral Stenosis	5,360,000	97	52	0.97	0.90	7.42
3	M	30	Mitral Stenosis	5,016,000	92	52	1.03	0.91	7.62
4	M	19	Mitral Regurgitation	4,624,000	84	47	1.01	0.90	7.59
5	F	25	Mitral Stenosis & Regurgitation	4,376,000	80	45	1.02	0.91	7.60
6	F	39	Adherent Pericardium; Mitral Stenosis	4,968,000	92	50	1.00	0.92	7.58
7	M	20	Mitral Stenosis & Regurgitation	4,720,000	85	48	1.01	0.90	7.45
8	F	18	Mitral Stenosis	4,856,000	86	49	1.00	0.88	7.42
9	M	50	Aneurysm of Thoracic Aorta; Aortic Regurgitation	4,840,000	88	48	0.99	0.90	7.36
10	M	25	Mitral Stenosis	5,304,000	98	52	0.98	0.92	7.30
11	F	33	Aortic Regurgitation	4,360,000	78	44	1.00	0.89	7.40
12	F	37	Mitral Stenosis; Aortic Regurgitation	4,560,000	82	45	0.98	0.90	7.32

TABLE V

CASES WITH COMPENSATED CARDIAC LESIONS (INCLUDING VISCOSITY DETERMINATIONS)

Case No.	Sex	Age	Lesion	Red Cells per c.mm.	Haemo-globin %	Haema-tocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ	Viscosity (Water = 1.0)
13	M	57	Aortic Regurgitation	5,024,000	88	50	0.99	0.87	7.47	5.8
14	F	47	Mitral Stenosis	5,400,000	100	53	0.98	0.92	7.42	6.2
15	M	19	Mitral Stenosis and Regurgitation	5,008,000	90	51	1.01	0.89	7.50	5.6
16	M	24	Mitral Stenosis, Aortic Regurgitation	4,700,000	83	46	0.97	0.88	7.40	4.8
17	F	48	Mitral Stenosis and Regurgitation	4,848,000	88	49	1.01	0.90	7.52	5.8
18	F	69	Chronic Degenerative Myocarditis, Complete Heart Block	5,280,000	96	50	0.94	0.91	7.38	6.0
19	F	42	Mitral Stenosis and Regurgitation	4,864,000	88	48	0.98	0.90	7.36	5.2
20	M	55	Aortic Stenosis and Regurgitation	5,040,000	90	49	0.97	0.89	7.45	5.4
			Average for the 20 cases =	4,892,000	88	49	0.99	0.90	7.45	5.6

tended to show a slight or moderate diminution in red cells, while a few cases (mostly of mitral stenosis) tended to show a slight increase in red cells above normal.

(c) The averages for haemoglobin percentage and colour index were only slightly below the corresponding averages for the normal subjects.

(d) The average blood viscosity (calculated from the second group of cases) was within normal limits, and was, in fact, practically similar to the average value for blood viscosity obtained in the 10 normal subjects in Table III.

The findings in the above series of 20 cases shown in Tables IV and V, apparently confirm what has been stated in the literature regarding fully compensated heart disease - namely, that the red cell count, haemoglobin percentage, and viscosity of the blood, are essentially normal. This investigation, however, supplies the additional information that the volume and diameter of the individual red blood cells are also normal.

Congestive Heart Failure.

The writer has studied 40 cases of congestive heart failure. The results for 36 of these cases are shown in Tables VI and VII, while those for the remaining four cases studied in greater detail are shown separately in their respective tables. In Table VI are shown the results for the 12 cases studied before viscosity determinations were commenced, while in Table VII, viscosity readings are included. Blood viscosity was also estimated in two of the four cases studied in greater detail.

While most of the patients that have been studied suffered from severe congestive cardiac failure, leading in some cases to death of the patient, for the sake of comparison, a few patients with less severe degrees of heart failure have also been included.

The 36 cases comprising Tables VI and VII are described later in the summary of the case reports. On both Tables, however, a note is given on each patient's condition, degree of dyspnoea (as far as could be gauged clinically, and which in patients with orthopnoea, indicates the degree of additional respiratory distress), cyanosis, and oedema, present at the time of making the observation, so as to help to correlate the results with the degree of the failure, and with any special feature of clinical condition.

Measurement of the degree of dyspnoea, cyanosis and oedema, as far as could be gauged from clinical observation, has been arbitrarily made as follows :-

Dyspnoea.

-	.....	Not present in bed.
+	.....	Slight.
++	.....	Moderate.
+++	.....	Severe.

Cyanosis

-	.....	None observed.
Slight	.....	Just visible bluish colour.
+	.....	Moderate.
++	.....	Marked.

Oedema.

Marked	.....	Pitting of entire leg and thigh - i.e., entire lower extremities involved.
Moderate	.....	Pitting of leg below knee, but slight or no pitting of thigh.
Slight	.....	Confined to ankles and feet.
Nil.	.....	Unrecognised oedema.

Additional data, such as ascites, anasarca, etc., have been noted where applicable.

TABLE VI

CASES OF CONGESTIVE HEART FAILURE

Case No.	Sex	Age	Diagnosis	Date	Condition	Dyspnoea	Cyanosis	Oedema	Red Cells per cmm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ	Result
21	M	65	Arterio-sclerosis; Myocardial Degeneration	18.2.29	Serious	+ +	+ +	Moderate	5,760,000	98	63	1.09	0.85	7.87	Discharged improved 6.4.29
				1.4.29	Improved	—	very sl.	Nil	5,016,000	90	50	0.99	0.89	7.50	
22	M	58	Chronic Interstitial Nephritis; Arterio-sclerosis; Myocardial Degeneration	20.3.29	Serious	+ + +	+ +	Marked; sl. lumbar back	5,480,000	90	61	1.11	0.82	7.98	
				7.5.29	Sl. improvement	+ +	+	Slight	5,032,000	84	53	1.05	0.83	7.72	Died 24.6.29
				21.6.29	Serious	+ + +	+ +	Moderate	5,600,000	90	61	1.09	0.80	7.90	
				23.6.29	Worse	+ + +	+ +	do.	5,820,000	92	64	1.10	0.79	7.90	
23	M	67	Arterio-sclerosis; Chronic Bronchitis and Emphysema	23.3.29	Serious	+ + +	+ +	Moderate	6,072,000	105	67	1.10	0.86	7.90	Discharged improved 1.5.29
				27.4.29	Improved	+	+	Nil	5,236,000	95	54	1.03	0.91	7.60	
24	M	38	Rheumatic and Syphilitic Heart Disease; Mitral Stenosis, Aortic Regurgitation	12.4.29	Serious	+ + +	+ +	Moderate; ascites	5,600,000	90	65	1.10	0.80	7.86	Died suddenly 28.4.29
25	F	30	Rheumatic Heart Disease; Mitral Stenosis; Auricular Fibrillation	13.4.29	Mild failure	+	+	Slight	5,120,000	86	53	1.03	0.84	7.64	Discharged improved 5.6.29
26	F	32	Rheumatic Heart Disease; Mitral Stenosis; Auricular Fibrillation	14.4.29	Serious	+ + +	+ +	Moderate; ascites	6,000,000	100	68	1.13	0.83	8.00	Went home against advice 21.4.29
27	F	36	Rheumatic Heart Disease; Mitral Stenosis, and Regurgitation	16.4.29	Mild failure	+	—	Slight	5,040,000	83	52	1.03	0.82	7.67	Discharged improved 1.6.29
28	F	19	Rheumatic Heart Disease; Mitral Stenosis and Regurgitation; Aortic Regurgitation	18.4.29	Very serious	+ + +	+	Anasarca; ascites	4,640,000	74	51	1.09	0.79	7.84	Died 26.4.29
29	F	48	Rheumatic Heart Disease; Mitral Stenosis and Regurgitation	24.4.29	Serious	+ + +	+	Anasarca; ascites	4,440,000	70	48	1.11	0.82	7.97	Discharged improved 8.6.29
				28.4.29	Sl. improvement	+ +	+	much less	5,000,000	88	54	1.08	0.88	7.81	
				15.5.29	Much better	—	very sl.	Slight (ankles)	4,768,000	85	49	1.02	0.89	7.56	
30	F	60	Chronic Bronchitis and Emphysema; Myocardial Degeneration; Auricular Fibrillation	25.4.29	Serious	+ + +	+ +	Moderate	6,428,000	108	72	1.14	0.84	8.10	Discharged improved 8.6.29
				23.5.29	Improved	+	+	Nil	5,570,000	99	59	1.06	0.89	7.80	
31	F	37	Rheumatic Heart Disease; Mitral Stenosis; Auricular Fibrillation	26.4.29	Mild failure	+	very sl.	Slight	5,000,000	85	48	0.96	0.85	7.48	Discharged improved 15.6.29
32	F	39	Exophthalmic Goitre; Auricular Fibrillation	15.6.29	Mild Failure	+	—	Slight	4,860,000	80	50	1.02	0.82	7.51	Discharged improved 1.8.29

TABLE VII

CASES OF CONGESTIVE HEART FAILURE (WITH VISCOSITY ESTIMATIONS)

Case No.	Sex	Age	Diagnosis	Date	Condition	Dyspnoea	Cyanosis	Oedema	Red Cells per cmm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ	Viscosity (Water = 1.0)	Result
33	F	25	Syphilitic Heart Disease; Aortic Regurgitation	18.6.29	F.serious	+ +	sl.	Slight	4,730,000	74	50	1.05	0.78	7.64	7.0	Transferred 26.6.29
34	M	21	Rheumatic Heart Disease; Mitral Stenosis, Auricular Fibrillation	19.6.29	Very serious	+ + +	+	Anasarca; Ascites	4,520,000	73	51	1.12	0.80	8.03	5.0	Died 20.6.29
35	M	50	Chronic Interstitial Nephritis; Arterio-sclerosis; Myocardial Degeneration; Emphysema	3.7.29	Serious	+ + +	+ +	Moderate	6,204,000	105	70	1.13	0.84	8.08	11.6	
			After oxygen...	do.	do.	easier	less	do.	5,800,000	100	63	1.08	0.86	7.82	9.6	Discharged himself, condition improved, 24.7.29
				20.7.29	Improved	very sl.	sl.	nil	5,372,000	96	54	1.00	0.90	7.56	6.5	
36	F	66	Syphilitic Heart Disease; Aortic Regurgitation	19.7.29	Serious	+ +	sl.	Slight	4,800,000	80	51	1.06	0.83	7.75	7.8	
				22.7.29	Fair	+	sl.	do.	4,688,000	78	49	1.04	0.83	7.59	7.4	
				29.7.29	Serious	+ +	sl.	Moderate	4,864,000	80	53	1.08	0.82	7.78	8.0	Died 1.8.29
				31.7.29	Worse, dying	+ + +	+	do.	5,128,000	82	55	1.07	0.79	7.78	8.6	
37	F	36	Chronic Parenchymatous Nephritis; Myocardial Degeneration	26.7.29	F.serious	+ +	sl.	Moderate	4,840,000	75	52	1.07	0.77	7.79	7.9	
				19.9.29	Worse	+ + +	do.	do. sl.lumbar back	4,244,000	60	45	1.06	0.70	7.74	7.1	Died 29.9.29
38	M	49	Chronic Bronchitis and Emphysema; Auricular Fibrillation	5.8.29	Serious	+ + +	+ +	Moderate; ascites	7,000,000	116	76	1.09	0.83	7.90	12.4	Transferred 22.11.29
39	M	31	Syphilitic Heart Disease; Aortic Regurgitation	30.8.29	Serious	+ +	sl.	Anasarca; sl.ascites	3,840,000	60	43	1.12	0.78	7.93	4.9	
				2.9.29	Slightly improved	+	sl.	Much less	4,496,000	74	49	1.08	0.82	7.80	7.3	Discharged himself, improved, 2.10.29
			Readmitted on 25.10.29													
				27.10.29	Serious	+ +	sl.	Marked	4,092,000	68	45	1.10	0.83	7.86	5.0	
				4.11.29	Improving	+	sl.	Less	4,464,000	76	48	1.07	0.85	7.60	7.0	Discharged improved 16.11.29
				14.11.29	Much better	—	—	Nil	4,240,000	74	41	0.96	0.87	7.42	5.8	

TABLE VII (Contd.)

Case No.	Sex	Age	Diagnosis	Date	Condition	Dyspnoea	Cyanosis	Oedema	Red Cells per cmm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ	Viscosity (Water = 1.0)	Result
40	M	69	Syphilitic Heart Disease; Aortic Regurgitation	14.9.29	Serious	+ +	+	Moderate	4,496,000	68	46	1.02	0.76	7.60	6.7	Discharged himself 22.11.29. Died at home
				9.10.29	Unchanged	+ + +	+	do.	4,560,000	70	47	1.03	0.76	7.58	7.0	
41	F	28	Rheumatic Heart Disease; Mitral Stenosis; Auricular Fibrillation	24.9.29	Serious	+ + +	+ +	Moderate; ascites	6,300,000	106	70	1.11	0.84	7.96	11.4	
			After oxygen....	do.	do.	less	less	do.	5,900,000	102	63	1.07	0.86	7.71	9.6	Discharged improved 30.11.29
				27.11.29	Much better	—	sl.	nil.	5,420,000	98	52	0.96	0.90	7.45	6.4	
42	F	48	Rheumatic Heart Disease. Mitral Stenosis; Auricular Fibrillation	26.9.29	F.serious	+ +	+	Moderate	5,600,000	90	57	1.02	0.80	7.50	8.0	Discharged herself 28.9.29
43	F	38	Rheumatic Heart Disease; Mitral Stenosis, and Regurgitation, Auricular Fibrillation	28.9.29	F.serious	+ +	+	Moderate	5,280,000	88	57	1.08	0.83	7.80	8.6	Discharged improved 15.11.29
				22.10.29	Improved	—	—	nil	4,700,000	82	47	1.00	0.87	7.44	5.4	
44	M	58	Rheumatic Heart Disease; Mitral Stenosis, Aortic Regurgitation; Chronic Bronchitis and Emphysema	8.10.29	Serious	+ + +	+ +	Moderate	5,700,000	96	64	1.12	0.84	7.98	10.4	
			After oxygen....	do.	do.	less	sl. less	do.	5,420,000	92	59	1.08	0.85	7.78	9.0	Died 11.10.29
				11.10.29	Worse, dying	+ + +	+ +	do.	5,800,000	96	64	1.10	0.83	7.87	10.2	
45	M	53	Aortic Regurgitation (Syphilitic); Chronic Bronchitis and Emphysema	12.11.29	Serious	+ + +	+ +	Moderate; sl.lumber back	5,540,000	92	60	1.08	0.83	7.77	9.0	Transferred 15.11.29
46	M	60	Chronic Bronchitis and Emphysema	15.11.29	Serious	+ +	+ +	Moderate	6,020,000	104	67	1.11	0.86	8.02	10.8	
				20.11.29	Worse	+ + +	+ +	do.	6,400,000	108	71	1.10	0.84	7.98	11.4	Died 21.11.29.
			After Oxygen...	do.	do.	sl. easier	sl. less	do.	5,872,000	102	63	1.07	0.86	7.76	9.8	

TABLE VII (Contd.)

Case No.	Sex	Age	Diagnosis	Date	Condition	Dyspnoea	Cyanosis	Oedema	Red Cells per cmm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ	Viscosity (Water = 1.0)	Result
47	F	24	Rheumatic Heart Disease; Mitral Stenosis and Regurgitation; Auricular Fibrillation	26.11.29	Serious	+ + +	+ +	Marked sl. back Ascites	5,500,000	94	61	1.11	0.85	7.95	9.2	
				2.12.29	F.serious	+ +	+ +	Moderate	5,612,000	95	62	1.10	0.85	7.89	9.4	Discharged improved 22.1.30
				1.1.30	Improving	+	sl.	Slight	5,026,000	88	52	1.03	0.87	7.75	6.9	
				19.1.30	Much better	—	very sl.	nil	4,800,000	86	47	0.98	0.88	7.52	5.6	
48	F	33	Rheumatic Heart Disease; Mitral Stenosis and Regurgitation	1.12.29	Serious	+ +	+	Moderate Sl.back	5,640,000	94	63	1.11	0.84	7.93	9.6	Discharged improved 18.1.30
				12.1.30	Improved	—	very sl.	nil	5,000,000	88	50	1.00	0.88	7.52	5.5	
49	F	60	Arterio-sclerosis; Aortic Regurgitation; Myocardial Degeneration	7.1.30	Serious	+ +	+	Moderate	5,240,000	88	56	1.06	0.83	7.76	8.2	Discharged improved 12.2.30
				9.2.30	Improved	very sl.	—	nil	4,692,000	82	46	0.98	0.87	7.49	5.1	
50	F	21	Infective Endocarditis; Rheumatic Heart Disease; Mitral Stenosis and Regurgitation, Aortic Regurgitation	15.1.30	Serious	+ +	—	Slight	3,500,000	35	28	0.80	0.50	7.12	3.8	Taken home 1.3.30. Died shortly afterwards
				21.2.30	Unchanged	do.	—	Moderate	3,164,000	31	25	0.78	0.49	7.08	3.5	
51	F	14	Rheumatic Heart Disease; Mitral Stenosis and Regurgitation	22.1.30	Serious	+ +	+	Moderate; ascites	5,200,000	85	57	1.09	0.81	7.85	8.4	Died suddenly 6.3.30
				25.2.30	Sl.worse	+ + +	+	Anasarca	4,400,000	72	49	1.11	0.81	7.90	5.5	
			After 1 cc. Novasurol....	26.2.30	Feels easier	+ +	+	Much less	5,000,000	82	54	1.08	0.82	7.80	7.5	
52	M	31	Infective Endocarditis; Rheumatic Heart Disease; Mitral Stenosis and Regurgitation, Aortic Regurgitation	10.2.30	Serious	+ +	—	Slight	3,684,000	44	31	0.84	0.59	7.15	4.2	Died 15.2.30

TABLE VII (Contd.)

Case No.	Sex	Age	Diagnosis	Date	Condition	Dyspnoea	Cyanosis	Oedema	Red Cells per cmm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ	Viscosity (Water = 1.0)	Result
53	M	64	Arterio-sclerosis; Aortic Regurgitation; Myocardial Degeneration	11.2.30	Serious	+ +	sl.	Moderate	4,484,000	70	48	1.07	0.78	7.75	7.5	Discharged himself 19.2.30
54	M	40	Infective Endocarditis; Rheumatic Heart Disease; Mitral Stenosis and Regurgitation; Aortic Regurgitation	1.3.30	Serious	+ +	sl.	Moderate	4,028,000	49	33	0.82	0.60	7.06	4.4	Died 14.3.30
55	M	65	Arterio-sclerosis; Aortic Stenosis and Regurgitation; Emphysema and Bronchitis, Auricular Fibrillation	18.4.30	Serious	+ + +	+ +	(Moderate; (Ascites	5,900,000	100	64	1.10	0.84	7.96	10.4	Discharged himself condition improved 29.5.30
				25.5.30	Improved	+	+	(Slight, no (ascites	5,240,000	94	53	1.01	0.90	7.62	6.3	
56	F	14	Rheumatic Heart Disease; Mitral Stenosis, Aortic Regurgitation; ? Adherent Pericardium	20.6.30	Serious	+ +	+	Moderate	5,400,000	84	54	1.00	0.77	7.52	7.7	Died 16.7.30

RESULTS IN CONGESTIVE HEART FAILURE

The results in the 36 cases of congestive heart failure, comprising Tables VI and VII, are analysed and described under the following headings :-

1. Volume Index and Average diameter of individual red cells.
2. Number of red cells, haemoglobin percentage, and average haemoglobin content of red cells (colour index).
3. Viscosity of the blood.

In addition to the above 36 cases, the four cases studied in greater detail, showing the effect of exacerbations and remissions of the heart failure, are described separately at the conclusion of the present analysis of the individual cases comprising Tables VI and VII.

1. Volume Index and Average Diameter of Erthrocytes.

The results for the volume and diameter of the individual red cells are conveniently described together. It was found that, according to the standard of differences suggested by Price-Jones (113) for 200 cells (the number measured by the writer), 19 of the 36 cases studied in Tables VI and VII (i.e., 53 per cent.) gave red cell diameter values in the stage of cardiac failure significantly increased above the average value of 7.48μ for the normal subjects, and the practically similar average value of 7.45μ for the compensated cases. The diameter value in each of these 19 cases was over 7.80μ - that is, it showed an increase of more than 0.32μ above the normal standard in

Table I. The volume indices in these 19 cases ranged from 1.09 to 1.14.

These 19 cases, all of which had a severe degree of cardiac failure, comprised the following :-

i. Twelve cases with valvular lesions, including three cases of mitral stenosis (all of which had auricular fibrillation), four cases of mitral stenosis and regurgitation (one with auricular fibrillation, and the other three with normal rhythm), three cases of aortic regurgitation combined with mitral stenosis, and two cases of aortic regurgitation with secondary mitral regurgitation.

ii. Three cases of chronic bronchitis and emphysema, two of which had auricular fibrillation.

iii. Two cases of arterio-sclerosis and high blood pressure.

iv. Two cases of chronic interstitial nephritis, arterio-sclerosis, and high blood pressure.

It was noted that two of the twelve cases with valvular heart lesions had co-existing chronic bronchitis and emphysema - namely, one of the cases of aortic regurgitation and one of the cases with a combined mitral and aortic lesion - and that chronic bronchitis and emphysema complicated one of the cases of arterio-sclerosis, and one of the cases of chronic interstitial nephritis.

Table VIII shows the corresponding readings for volume index and average diameter of the red cells in these 19 cases :-

TABLE VIII

Corresponding Volume Indices and Average Diameters of Red Cells in 19 cases of severe congestive Heart Failure.

Case No.	Volume Index	Diameter in μ	
21	1.09	7.87	
22	1.11	7.98	
23	1.10	7.90	
24	1.10	7.86	
26	1.13	8.00	
28	1.09	7.84	
29	1.11	7.97	
30	1.14	8.10	
34	1.12	8.03	
35	1.13	8.08	
38	1.09	7.90	
39	(1) 1.12	7.93	
	(2) 1.10	7.86	..... on readmission
41	1.11	7.96	
44	1.12	7.98	
46	1.11	8.02	
47	1.11	7.95	
48	1.11	7.93	
51	1.09	7.85	
55	1.10	7.96	
Average	1.11	7.94	

The average results in these 21 cases show an increase in volume index and mean red cell diameter of 12 per cent., and 0.46 μ, respectively, above the average values for the normal subjects in Table I, and of 12 per cent., and 0.49 μ above the average values for the cases of fully compensated heart disease, comprising Tables IV and V.

Ten of these patients were discharged improved, and it was noted that improvement in clinical condition was accompanied by a reduction in volume and diameter of the red cells which, with one exception, returned to normal values. This is illustrated in Table IX.

T A B L E IX

REDUCTION IN VOLUME AND DIAMETER OF ERYTHROCYTES WITH CLINICAL IMPROVEMENT

Case No.	Condition	Volume Index	Diameter in μ
21	(Serious	1.09	7.87
	(Improved	0.99	7.50
23	(Serious	1.10	7.90
	(Improved	1.03	7.60
29	(Serious	1.11	7.97
	(Improved	1.02	7.56
30	(Serious	1.14	8.10
	(Improved	1.06	7.80
35	(Serious	1.13	8.08
	(Improved	1.00	7.56
39 (2)	(Serious	1.10	7.86
	(Improved	0.96	7.42
41	(Serious	1.11	7.96
	(Improved	0.96	7.45
47	(Serious	1.11	7.95
	(Improved	0.98	7.52
48	(Serious	1.11	7.93
	(Improved	1.00	7.52
55	(Serious	1.10	7.96
	(Improved	1.01	7.62

The exceptional case was Case 30, a patient with congestive heart failure secondary to chronic bronchitis and emphysema, who exhibited a probable, and almost significant, increase in average size of the erythrocytes above normal, when the cardiac failure had subsided.

Of the remaining nine patients of Table VIII, one (Case 26) discharged herself against hospital advice. In this case, only one set of observations was made. Another patient (Case 38) - in whom also only one set of observations was made - was transferred to another hospital for special reasons.

The other seven patients died, and in three of these cases (Nos. 22, 44 and 46) it was noted that at observations made just before death, when cardiac failure was more advanced, the values for volume index and mean diameter of the red cells were not higher than those obtained at the time of admission to hospital. Case 22 had an average red cell diameter of 7.98 μ and a corresponding volume index of 1.11 shortly after admission, while the corresponding readings on the day before he died, were 7.90 μ and 1.10, respectively. In Case 44, the readings were 7.98 μ and 1.12 for red cell diameter and volume index respectively, at the time of admission, and 7.87 μ and 1.10 on the day of his death, and in Case 46, the readings were 8.02 μ and 1.11 on admission, and 7.98 μ and 1.10 (taken before an oxygen administration) the day before the patient died. Another patient who died (Case 36), but whose results do not belong to Table VIII, also exhibited this failure of the red cells to show a greater degree of enlargement with proximity of death.

The remaining 17 (47 per cent.) of the 36 cases described in Tables VI and VII, did not show average red cell diameters significantly raised above normal, and had volume indices invariably below 1.09. According to the statistical standard of

differences, these 17 cases comprised six cases with probable, although not conclusively real, increases in diameter value above normal, eight cases with normal mean diameters, and three cases with mean diameters significantly reduced below normal.

The six cases of congestive heart failure with probable increases in mean red cell diameter above the normal average, were Cases 36, 37, 43, 45, 49 and 53. The conditions represented in these cases were (i) aortic regurgitation in four cases, due in two cases to syphilis (one of which had co-existing emphysema and bronchitis), and in the other two cases to arterio-sclerosis, in which syphilis was not a factor (emphysema and chronic bronchitis being also present in one of these cases); (ii) chronic parenchymatous nephritis, in one case, and (iii) mitral stenosis with auricular fibrillation, in one case. A severe, or moderately severe, degree of heart failure was present in these patients, two of whom died in hospital.

Table X gives the corresponding readings for volume index and mean diameter of red cells in these six cases :-

TABLE X

Case No.	Volume Index	Diameter in μ
36	1.06	7.75
	1.08	7.78
	1.07	7.78
37	1.07	7.79
	1.06	7.74
43	1.08	7.80
45	1.08	7.77
49	1.06	7.76
53	1.07	7.75
Average	1.07	7.77

It should be mentioned that the diameter value of 7.80μ in Case 43 indicated almost a significant increase above the normal average.

The eight cases with normal diameter values according to the standard of differences, were Cases 25, 27, 31, 32, 33, 40, 42 and 56. Of these eight cases, four (Cases 25, 27, 31 and 32) were, according to their clinical conditions, cases of mild heart failure, while the remaining four were cases of more advanced heart failure. The lesions in these last mentioned four cases were aortic regurgitation (syphilitic) in Cases 33 and 40, mitral stenosis in Case 42, and mitral stenosis combined with aortic regurgitation in Case 56.

Table XI gives the corresponding readings for volume and diameter of the erythrocytes in the four cases of cardiac

failure with mild symptoms :-

T A B L E XI

Case No.	Volume Index	Diameter in μ
25	1.03	7.64
27	1.03	7.67
31	0.96	7.48
32	1.02	7.51
Average	1.01	7.57

It will be seen that the average diameter of the red corpuscles in Table XI shows no deviation from the average normal diameter in Table I, according to the standard of differences, and also that the average volume index is practically similar to that for the normal subjects.

The corresponding readings for volume index and mean diameter value of the erythrocytes in the four cases with more pronounced manifestations of heart failure are given in Table XII.

T A B L E XII

Case No.	Volume Index	Diameter in μ
33	1.05	7.64
40	(1.02 (1.03	7.60 7.58
42	1.02	7.50
56	1.00	7.52
Average	1.02	7.56

As in the case of Table XI, the average results in Table XII must be regarded as showing no deviation from those of the normal subjects in Table I.

The three cases with diminution in volume and diameter of the red blood cells below normal, were Cases 50, 52 and 54 of infective endocarditis, superimposed on chronic valvular disease. Cardiac failure was present in each case, with dyspnoea, orthopnoea, congestion of the lungs, enlargement of the liver, and oedema. Blood cultures in each case showed the presence of streptococci. While both the volume index and mean diameter value of the corpuscles were below normal in these cases, it was noted that the diameters were not reduced to the same extent as the volumes. It should be mentioned, however, that the presence of poikilocytosis in these diseased bloods, made it difficult to obtain good samples for the measurement of cell diameters, and probably introduced a greater degree of inaccuracy in these measurements than in those of other cases.

Table XIII gives the corresponding volume indices and average diameters of the red cells in these cases :-

T A B L E XIII

Case No.	Volume Index	Diameter in μ
50	0.80 0.78	7.12 7.08
52	0.84	7.15
54	0.82	7.06
Average	0.81	7.10

A marked degree of oedema was present in seven of the 53 per cent. of cases comprising Tables VI and VII which exhibited significantly enlarged red cells above normal. These were Cases 22, 28, 29, 34, 39, 47 and 51, and in five of these cases, the oedema amounted to general anasarca. In Cases 29, 39 and 51 (three of the cases with anasarca), the effects of subsidence of oedema following a satisfactory diuresis were studied, and it was found that this was associated with a slight diminution in volume index and mean diameter value of the red cells, which was in each case associated with a coincident increase in red cell count and haemoglobin percentage. (The latter point is further referred to in the section dealing with the number of erythrocytes and the haemoglobin percentage.)

These changes in number and size of red cells, and percentage of haemoglobin, occurring with diuresis, in cases exhibiting gross oedema, are illustrated in Figure 1, relating to Case E.W., one of the four cases studied with more frequent determinations.

It was also noted, from a further study of Case 29, and of Case 39 during the latter's second stay in hospital, that while a slight diminution in volume and diameter of the red blood cells occurred with subsidence of oedema following diuresis, a return to normal values was not present until further clinical improvement had occurred and "compensation" was practically re-established. This further diminution in volume and diameter of the erythrocytes was associated with a decrease in their number and in the haemoglobin percentage. Regarding Case 39's first stay in hospital, no further

observations were made after 2.9.29, as the writer was away.

After the first set of observations in Cases 35, 41 and 44, taken shortly after admission, and after the second set of observations in Case 46, taken six days after admission, a further set of blood observations was made immediately following an administration of oxygen. The latter, administered by the nasal catheter method, was given until some relief occurred in dyspnoea and cyanosis.

In all the cases, there was a diminution in total red cell volume (as shown by the haematocrit readings), together with a slight, but consistent, diminution in the volume index and average diameter of the individual red cells. On the basis of statistical differences, none of the cases showed a significant decrease in diameter value, two cases (Nos. 35 and 41) showed probable decreases, and one of the remaining cases (No. 46) showed only an approximately probable decrease. It is nevertheless considered, as further referred to in the discussion of the results, that there has been a tendency to reduction in the volume and diameter of the corpuscles with oxygen administration, particularly when this is related to the coincident diminution in erythrocyte count and blood viscosity.

It has been noted that, except possibly in the cases of infective endocarditis, a fairly constant correspondence existed between the volume indices and the average diameters of the red cells in the cases shown in Tables VI and VII.

Rossdale (116) has pointed out that where there is incomplete

centrifugalization of blood, a high volume index may sometimes be obtained, owing to the haematocrit reading being too high. In such cases, the red cell diameter would probably not show a corresponding increase, so that a raised volume index with a normal diameter value may indicate that the former is too high. On the other hand, a raised volume index with a corresponding increase in diameter value would probably indicate a true reading, which may be applied to the results in this investigation, in so far as noticeable increases in volume index above the normal standard (usually increases of about 10 per cent. or more) have been associated with real and significant increases above normal in mean diameter value, according to the standard of differences.

By dividing the results into groups showing significant and probable increases in size of the erythrocytes above normal, no deviation in size of the cells from normal, and diminution in size of the cells below normal, the writer considers that a more comprehensive picture of possible variations occurring in size of red blood cells in congestive heart failure, as shown in this work has been presented. It was also of interest to correlate the results with the lesions present, and with the clinical condition of the patient at the time of making the observations, as in this way, more information was obtained.

It was found, for example, that although certain exceptions occurred, significant increases in the size of red cells above normal in congestive heart failure due to valvular lesions, were

more commonly found in connection with a mitral lesion (especially stenosis) than with an aortic lesion such as aortic regurgitation, except when the latter was combined with mitral stenosis, or was associated with co-existing chronic bronchitis and emphysema. Further, congestive heart failure secondary to a pulmonary affection such as a combination of chronic bronchitis with emphysema, was associated with significant increases in size of the cells above normal, while a condition of infective endocarditis in patients exhibiting cardiac failure was associated with a diminution in size of the erythrocytes below normal.

Regarding the clinical condition of the patient, it was found that, generally speaking, a serious condition, indicating a severe degree of heart failure, was more commonly associated with enlargement of the red cells than heart failure with mild symptoms, although in this connection, exceptions were again present, four cases with severe circulatory symptoms, for example, having exhibited normal values for size of the corpuscles.

An attempt is made in the discussion of the results to explain the variations in the size of red blood cells in congestive heart failure - resulting in the absence of a constant ratio, as previously mentioned, between the severity of the cardiac failure and the degree of corpuscular enlargement - and also to indicate the general significance of the type of lesion, in relation to the results.

The foregoing findings with regard to the volume and diameter of the red cells in the 36 cases shown in Tables VI and VII, may be summarised as follows :-

1. (a) Nineteen cases (53 per cent.) of severe congestive heart failure gave average results for volume index and mean diameter value of the red cells, of 1.11 and 7.94μ respectively. An increase is shown of 12 per cent. and 0.46μ above the average results for volume and diameter of erythrocytes in 12 healthy subjects, and of 12 per cent. and 0.49μ above the average results for a series of 20 cases of compensated heart disease. According to a standard of differences based on statistics for 200 red cells (the number measured in this work for diameters), a real and significant increase above normal has apparently been present in the average size of the red cells in these 19 cases.

(b) These 19 cases comprised 12 cases with valvular lesions (three with mitral stenosis, four with mitral stenosis and regurgitation / three with a combination of mitral stenosis with aortic regurgitation, and two with aortic regurgitation and secondary mitral regurgitation); three cases of chronic bronchitis and emphysema; two cases of arterio-sclerosis and high systemic blood pressure, and two cases of chronic interstitial nephritis, arterio-sclerosis and high blood pressure. It was observed that chronic bronchitis and emphysema were associated with

two of the valvular heart cases (one of the cases of aortic regurgitation with secondary mitral regurgitation, and one of the cases with combined aortic and mitral lesions), one of the cases of arterio-sclerosis and one also of the cases of chronic interstitial nephritis.

2. The remaining 17 cases (47 per cent.) had red cells apparently not significantly increased in size above normal, and of these cases :-

(i) Six gave average results of 1.07 and 7.77μ for volume index and mean diameter value respectively, which, according to the standard of differences, are taken to represent probable, although not conclusively real, increases in average size of the corpuscles above normal. These six cases of congestive heart failure comprised four cases with aortic regurgitation and secondary mitral regurgitation (in one of which chronic bronchitis and emphysema were present), one case with chronic parenchymatous nephritis and one case with mitral stenosis. These patients exhibited severe or moderately severe degrees of heart failure.

(ii) Eight cases (comprising four cases of congestive heart failure with mild symptoms, and four cases with severe symptoms) gave average results of 1.01 and 7.57μ for volume index and mean diameter of the erythrocytes in the cases of mild heart failure, and 1.02 and 7.56μ for volume index and mean diameter in the group of cases with more pronounced heart failure. Both sets of average results showed no

deviation from the normal averages obtained in Table I.

In the group with mild symptoms, three were cases of valvular heart disease, and the fourth a patient with exophthalmic goitre in whom cardiac failure associated with auricular fibrillation had occurred. In the second group of cases with severe circulatory symptoms, two were cases of aortic regurgitation with secondary mitral regurgitation, one was a case of mitral stenosis with auricular fibrillation, and the fourth was a case of mitral stenosis in combination with aortic regurgitation.

(iii) Three cases gave average results of 0.81 and 7.10 μ for volume index and average diameter value of the red cells, respectively, which represented significant decreases below normal. These three patients suffered from failure of compensation associated with chronic valvular disease, on which, however, was superimposed a condition of infective endocarditis, the latter confirmed by positive blood cultures.

3. Clinical improvement, occurring in 10 of the 19 patients who had significant increases in the size of the red cells above normal, was associated with a diminution in volume and diameter of the cells with a return to normal values in nine of the cases. In the remaining case - a patient with heart failure secondary to emphysema and chronic bronchitis - the size of the erythrocytes, even after cardiac failure had subsided, showed a probable and almost significant increase above normal.

4. Proximity of death appeared to have a frequent tendency to inhibit further enlargement of the red cells.

5. The 53 per cent. of cases of Tables VI and VII exhibiting significantly enlarged red cells above normal, included seven cases with gross oedema, in five of which general anasarca was present. Subsidence of oedema following diuresis was, as shown in three of the cases with anasarca, associated with a slight diminution in volume index and mean diameter value of the red cells, and a coincident increase in each case, in erythrocyte count and haemoglobin percentage. Later observations on two of these three cases showed that normal values for cell volume and diameter were obtained only after further clinical improvement, and with re-establishment of a state of "compensation".

6. The effect of the administration of oxygen, studied in four cases, was to cause a diminution in total red cell volume, associated with a slight but consistent diminution in the values for volume and diameter of the individual erythrocytes.

7. A fairly close correspondence was found to exist between the volume indices and the cell diameters, and the latter were significantly increased above the normal standards in all cases where the red cells showed an increase in volume of about 10 per cent. or more, above the normal average value in Table I.

2. Number of Red Cells, Haemoglobin Percentage, and Haemoglobin Content of Red Cells.

Of the 36 cases studied in Tables VI and VII, it was found that 20 cases (55 per cent.) gave red cell counts in the peripheral capillary blood in the stage of heart failure, above the average reading of 5,000,000 for the normal subjects, with which the average count of 4,892,000 per c.mm. for the compensated cardiac cases may be considered practically to correspond. The counts in these 20 cases ranged from 5,200,000 to 7,000,000 red cells per c.mm. of blood.

It was noted that of these 20 cases, 15 were included in Table VIII, as showing raised volume indices and significant increases in average diameter of the red cells above normal. Three of the remaining five cases showed only probable increases in diameter of the erythrocytes, with relatively lower volume indices, while the other two cases had normal values for volume and diameter. While therefore most of the cases with raised erythrocyte counts also had individual red cells increased in volume and diameter above the normal average values, exceptions occurred, as, for example, in Cases 42 and 56 with normal values for volume index and average cell diameter, where the counts were 5,600,000 per c.mm., and 5,400,000 per c.mm., respectively.

These 20 cases of congestive heart failure with raised erythrocyte counts comprised 13 cases with valvular lesions, three cases of chronic bronchitis and emphysema, two cases of

arterio-sclerosis and high blood pressure, and two cases of chronic interstitial nephritis, arterio-sclerosis and high blood pressure. It was found that eight of the cases of valvular disease, together with the seven cases comprising the other groups, made up the 15 cases, in which, as previously stated, increases above normal in volume and diameter of the corpuscles were present.

A more detailed analysis of the 13 cases with valvular lesions showed that three cases had mitral stenosis (all of which had auricular fibrillation), four cases had mitral stenosis and regurgitation (two with auricular fibrillation, and the remaining two with normal rhythm), three had combined organic valvular lesions (mitral stenosis and aortic regurgitation), and three cases had aortic regurgitation with secondary mitral regurgitation. It was noted that two of the three cases of aortic regurgitation had co-existing emphysema with bronchitis, and that the latter condition was present also in one of the cases with combined organic valvular lesions, one of the cases of arterio-sclerosis, and one of the cases of chronic interstitial nephritis.

The highest red cell counts - those from 6,000,000 to 7,000,000 per c.mm. - were given by two cases of mitral stenosis (Nos. 26, 41), the three cases of chronic bronchitis and emphysema (Nos. 30, 38, 46), the case of arterio-sclerosis associated with emphysema and bronchitis (No. 23), and the case of chronic interstitial nephritis also associated with emphysema and bronchitis (No. 35).

The haemoglobin percentages in the 20 cases showing increase in the number of red cells above 5,000,000 per c.mm. have ranged from 85 to 116 per cent. Taking the average normal value of 96 per cent. (Table I) as the standard for comparison, it was noted that in only nine of the cases with raised red cell counts above normal was the haemoglobin percentage above normal, the remainder of the cases having haemoglobin percentages either at, or - as was more frequently the case - below the normal standard. In fact, in four cases with counts over 5,000,000 per c.mm., the haemoglobin readings were below 90 per cent. It appeared that, generally speaking, these cases of congestive heart failure exhibited relatively high red cell counts compared to the haemoglobin percentages, which were apparently not increased to the same extent as the counts.

It was noted in eight of the ten patients of Table IX, who were discharged improved, and in Cases 43 and 49 of Table X, in whom observations were also made where improvement had occurred, that a diminution in red cell count and haemoglobin percentage occurred with clinical improvement, more marked in the count than in the haemoglobin percentage. The remaining two patients of Table IX who were discharged improved (Cases 29 and 39) were patients who had exhibited gross oedema, and apparently had special results, regarding erythrocyte count and haemoglobin percentage, which will be referred to later.

It was further noted that in the subsequent stage of

improvement, the red cell counts were normal or only slightly diminished below normal. In three cases, however, (Nos. 30, 35, 41) there appeared to be a tendency for the erythrocyte count to remain raised above the normal standard, when improvement from cardiac failure had occurred.

Table XIV shows the reduction occurring in red cell count and haemoglobin percentage, with clinical improvement :-

TABLE XIV

Case No.	Condition	Red Cells per c.mm.	Haemoglobin %
21	Serious	5,760,000	98
	Improved	5,016,000	90
23	Serious	6,072,000	105
	Improved	5,236,000	95
30	Serious	6,428,000	108
	Improved	5,570,000	99
35	Serious	6,204,000	105
	Improved	5,372,000	96
41	Serious	6,300,000	106
	Improved	5,420,000	98
43	Fairly serious	5,280,000	88
	Improved	4,700,000	82
47	Serious	5,500,000	94
	Improved	4,800,000	86
48	Serious	5,640,000	94
	Improved	5,000,000	88
49	Fairly serious	5,240,000	88
	Improved	4,692,000	82
55	Serious	5,900,000	100
	Improved	5,240,000	94

Increase in severity of clinical condition was, on the other hand, usually associated with increase in red cell count and haemoglobin percentage, more marked in the former than in the latter, as, for example, in Cases 22, 44 and 46. Case 37, however, a patient diagnosed as chronic parenchymatous nephritis, showing secondary congestive heart failure, appeared to be an exception to this rule, in that both the count and haemoglobin percentage fell with increased severity of the heart failure.

The effect of oxygen on red cell count and haemoglobin percentage was studied in four of the patients with marked cyanosis to whom it was administered, and in whom the effect on the volume and diameter of the cells has previously been noted. It was observed that in all four cases the result of the inhalation of oxygen (which relieved dyspnoea and reduced cyanosis) was a slight, but consistent, reduction in red cell count and percentage of haemoglobin.

Of the 16 cases (45 per cent.) which gave red cell counts approximately of/5,000,000 or under, four were the cases of mild heart failure (Nos. 25, 27, 31, 32), and the remainder were patients whose clinical conditions were more serious. These were Cases 28, 29, 33, 34, 36, 37, 39, 40, 50, 52, 53 and 54.

Cases 28, 29, 34 and 39 had gross oedema, and a study of Cases 29 and 39 (the two cases of Table IX with special results, as previously mentioned) reveals a lowered erythrocyte count and haemoglobin percentage in the oedematous stage, and an increased count and haemoglobin percentage, when subsidence of oedema occurred after diuresis. Following this increase after

diuresis, a slight decrease in red cells and haemoglobin took place with continued clinical improvement.

Case 51 on 26.2.30 also illustrates the increase in cell count and haemoglobin percentage with diminution in oedema, the latter resulting from an intramuscular injection of novasurol, which increased the urinary output from 18 oz. to 100 oz. in 24 hours.

It should be mentioned that while the markedly oedematous stage in the above mentioned cases was associated with a diminished red cell count, two cases (Nos. 22 and 47) with "marked" oedema, as indicated in Table VIII, had red cell counts of over 5,000,000.

In patients with moderate oedema, the blood, as a general rule, was observed to exhibit red cell counts over 5,000,000 per c.mm., which in some cases reached 6,000,000 per c.mm. and over.

Cases 50, 52 and 54 were the patients suffering from the cardiac type of infective endocarditis, and presenting symptoms and signs of failing compensation. A severe secondary anaemia was present in these cases, the haemoglobin percentages being greatly reduced below normal. It was noted that in two of these cases, cyanosis was absent, and that in the remaining case, it was only very slight.

Cases 33, 36 and 40 had aortic regurgitation due to syphilitic infection. A slight diminution in the number of red cells was present in these cases, together with a relatively greater diminution in haemoglobin percentage. A tendency to concealment

of the oligocythaemia was, however, observed in Case 36, with increase in severity of the heart failure, when an increase was found to occur in red cell count, which gave a reading of slightly over 5,000,000 per c.mm.

Case 53 had aortic regurgitation associated with arteriosclerosis. Syphilis was not a factor in this case. A "secondary anaemia" type of blood picture was also exhibited in this case, the haemoglobin percentage being reduced to a greater degree than the red cell count.

Case 37 was the patient with chronic parenchymatous nephritis and secondary congestive heart failure. At the first blood examination, this patient had a haemoglobin reading of 75 per cent., indicating a moderate anaemia, although the red cell count was only slightly below the normal standard. At the time of the second observation, when, clinically, her condition of heart failure was worse, a noticeable diminution in both the number of erythrocytes and the percentage of haemoglobin - more marked in the latter than in the former - was found to be present, the readings being 60 per cent. for haemoglobin, and 4,244,000 for cell count. As previously stated, this appeared to be contrary to the general tendency to an increase in the number of red cells, and slightly also in haemoglobin percentage with increase in severity of the cardiac failure. The significance of the apparently exceptional blood count in Case 37, at the time of the second observation, is discussed later.

Regarding the complement of haemoglobin of the individual red cells in congestive heart failure, it was found that an average value for colour index, calculated from 41 readings taken in the stage of heart failure, in 33 of the cases in Tables VI and VII, was 0.81. In calculating this average colour index, it was considered that the cases of infective endocarditis should not be included, owing to their exceptionally low readings. The range for colour index values in the above mentioned 33 cases was from 0.70 to 0.86, in the stage of cardiac failure.

On comparing the above average colour index of 0.81 with that of 0.95 obtained for the normal subjects, it appeared that the average haemoglobin content of the red cells in congestive heart failure was lower than normal. On comparing it also with the average colour index of 0.90 for the 20 cases of fully compensated heart disease, the average corpuscular haemoglobin content for the cases of heart failure also showed some reduction, although not to the same extent as in the case of the normal subjects.

A relatively lowered colour index was apparently a characteristic feature of a condition of congestive heart failure. While this was due in a few cases to the fact that the blood changes were those of a secondary anaemia, in many other cases, where the erythrocyte counts were over 5,000,000 per c.mm., the tendency for the average haemoglobin content of the red cells to be somewhat lower than the average normal value resulted from

the fact that in these cases the number of the red cells was relatively high compared to the haemoglobin percentage, the latter being, generally speaking, increased to a less degree than the red cell count.

A point which, it is considered, should be mentioned, is the manner in which the colour index has been related to the volume index and mean diameter of the red cells. It was observed that the colour index was always fractional - in no case reaching unity - in association with the raised values for volume and diameter of red cells above normal. In other words, it appeared that the over-sized erythrocytes in congestive heart failure were not accompanied by a correspondingly high individual haemoglobin content. Further, the diminution in volume and diameter of the cells occurring with clinical improvement (as shown in Table IX) was associated with a slight increase in the value for colour index, as seen, for example, in Cases 21, 35, 41 and 47. The relationship between the size of the individual erythrocytes and their content of haemoglobin is illustrated by the graphs relating to the four cases studied in greater detail, where it will be seen that the curves for volume index and mean diameter value, and the curve for colour index, are not direct in their ratio, but prove at times to be inverse.

The principal findings in this section may be summarised as follows :-

1. An increase in red cell count above the average value of approximately 5,000,000 for the normal subjects and compensated heart cases, was present in the peripheral blood of 20 of the 36 cases (55 per cent.) of congestive heart failure, shown in Tables VI and VII.

The counts in these cases ranged from 5,200,000 to 7,000,000 red cells per c.mm.

2. Of these 20 cases, 15 were included in the 21 cases described in the previous section, as exhibiting significant increases in raised volume indices and significant increases in average diameter of the individual erythrocytes above normal. Three of the remaining five cases showed probable increases in size of the cells above normal, while the other two cases had red cells which, according to the standard of differences, did not show any deviation in diameter from the normal, and which also gave a normal value for volume index.

3. The 20 cases of congestive heart failure with raised erythrocyte counts comprised 13 cases with valvular lesions (three with mitral stenosis, four with mitral stenosis and regurgitation, three with aortic regurgitation combined with mitral stenosis, and three with aortic regurgitation and secondary mitral regurgitation); three cases of chronic bronchitis and emphysema; two cases of arterio-

sclerosis with high systemic blood pressure, and two cases of chronic interstitial nephritis, arterio-sclerosis and high blood pressure. It was noted that chronic bronchitis and emphysema were present in two of the cases of aortic regurgitation with secondary mitral insufficiency, one of the cases with combined valvular lesions, one of the cases of arterio-sclerosis, and one of the cases of chronic interstitial nephritis.

4. The highest red cell counts - those from 6,000,000 to 7,000,000 per c.mm. - were given by two cases of mitral stenosis, the three cases of chronic bronchitis and emphysema, the case of arterio-sclerosis with co-existing emphysema and bronchitis, and the case of chronic interstitial nephritis, with a similar co-existing pulmonary affection.

5. The haemoglobin values in the above 20 cases with raised erythrocyte counts above the normal average of 5,000,000, have ranged from 85 to 116 per cent. In nine cases, the readings were above the normal average of 96 per cent. obtained in Table I; in seven cases, they were from 90 to 96 per cent., while in the remaining four cases, they were below 90 per cent. The red cell counts in these cases were, generally speaking, relatively more increased than were the haemoglobin percentages.

6. As shown in Table XIV, improvement from congestive heart failure in 10 cases was associated with a decrease in

red blood cell count, and, to a less extent, in percentage of haemoglobin. Increase in severity of the cardiac failure was, on the other hand, usually associated with increase in red cell count, and slightly also in haemoglobin percentage, except in Case 37, of chronic parenchymatous nephritis and secondary heart failure, where, with increase in the latter, there occurred a diminution in both the number of red cells and the haemoglobin percentage.

7. The administration of oxygen - given because of well-marked cyanosis - was in four cases where its effect was studied, found to reduce cyanosis, and to cause a slight, but consistent, diminution in the number of red cells per c.mm., and in the haemoglobin percentage.

8. The 45 per cent. of cases with red cell counts of 5,000,000 or under, comprised four cases of mild heart failure and 12 cases of severe, or moderately severe, cardiac failure. The count was practically at the normal standard in the four cases of mild failure (although slightly increased in one of them) and diminished below normal in the 12 cases of more pronounced heart failure.

9. These 12 cases with diminished erythrocyte counts, comprised the three cases of infective endocarditis, the case of chronic parenchymatous nephritis (in which the diminution in cell count was mainly shown at the second examination), four cases of aortic regurgitation, and four cases of valvular disease, with general anasarca.

10. It was observed, in two of the last-mentioned cases exhibiting gross oedema, that while a diminished erythrocyte count and haemoglobin percentage were present in the oedematous stage, an increase in red cells and haemoglobin characterised subsidence of oedema with diuresis. This appeared to indicate that the diminution in red cell count and haemoglobin percentage in the stage of gross oedema was a relative one, depending probably on the state of the blood in this stage, a point which is described later.

11. The blood changes in the other cases described under (9) were those of secondary anaemia, oligocythaemia being constantly less marked than reduction in haemoglobin percentage.

12. (a) A marked degree of anaemia was associated with infective endocarditis and heart failure, where, in one case, a haemoglobin percentage as low as 31 was recorded. Mild or moderate degrees of anaemia were present in the four cases of aortic regurgitation (three due to syphilis, and the fourth to arterial disease of non-syphilitic origin), and in the case of chronic parenchymatous nephritis with secondary cardiac failure.

(b) In the last-mentioned case of chronic parenchymatous nephritis with cardiac failure, diminution in both the red cell count and haemoglobin percentage occurred, with increase in severity of the cardiac failure. This was contrary to the more usual finding, under such conditions, of an increase in

count and - to a less extent - in haemoglobin percentage, shown even by one of the above cases with a "secondary anaemia" type of blood picture - namely Case 36, of aortic regurgitation - where, with increase in the heart failure, there was a tendency to concealment of the oligocythaemia by a rise in the erythrocyte count to a little over 5,000,000 cells per c.mm.

13. The values for colour index in the stage of heart failure with venous congestion in 33 of the cases in Tables VI and VII - that is, excluding the cases of infective endocarditis - have ranged from 0.70 to 0.86. An average value, calculated from 41 readings in these 33 cases, was found to be 0.81, which, compared with the average value of 0.95 for the normal subjects, apparently showed a reduction, and which was also slightly lower than the average value of 0.90 for the compensated cases.

The lowest values for colour index in the Tables were obtained in the three cases of circulatory failure occurring in the cardiac type of infective endocarditis, the readings being 0.50, 0.59 and 0.60.

14. Apart from cases where the blood changes were those of secondary anaemia, the tendency to relatively decreased colour index values in cases of severe congestive failure showing raised erythrocyte counts above 5,000,000, was apparently due to the fact that in such cases the red cell

counts were relatively more increased than were the haemoglobin percentages.

15. The over-sized erythrocytes in congestive heart failure were not related to correspondingly high values for colour index, the latter being always fractional, and in no case reaching unity. The colour index did not vary directly with the volume and diameter of the corpuscles, the results indicating that, at times, the average haemoglobin content of the corpuscles stood in inverse ratio to the volume index and mean diameter value.

Viscosity of the Blood.

It has been previously stated that the average viscosity values for 10 normal subjects and eight compensated heart cases, as determined by the Hess viscosimeter were found to be 5.32 and 5.60, respectively, and that viscosities above 6.0 or below 4.0, whether for male or female, could be reasonably regarded as being abnormal.

The viscosity of the blood was determined in the 24 cases described in Table VII, and it was found that 20 cases (83 per cent.) had viscosity readings over 6.0, three cases had readings between 4.0 and 5.0, and the remaining case had a reading below 4.0. It should be mentioned, however, that in one of these 83 per cent. of cases (No. 39), a relatively lowered viscosity value at one time of 4.9 was present.

In addition to these 24 cases of Table VII, viscosity determinations were also made on two of the four cases studied in more detail.

The viscosity values in the above-mentioned 20 cases ranged from 6.7 to 12.4. It appeared that higher viscosity values were generally present in those cases with higher values for red cell count, haemoglobin percentage and volume and diameter of the individual red cells. This is shown in Table XV, which gives the results in 10 of the cases :-

TABLE XV

The viscosity of the blood in relation to erythrocyte count, haemoglobin percentage, and size of red cells, in nine cases of severe congestive heart failure :-

Case No.	Viscosity (Water = 1.0)	Red Cells per c.mm.	Haemo-globin %	Volume Index	Diameter in μ
35	11.6	6,204,000	105	1.13	8.08
38	12.4	7,000,000	116	1.09	7.90
41	11.4	6,300,000	106	1.11	7.96
44	10.4 10.2	5,700,000 5,800,000	96 96	1.12 1.10	7.98 7.87
45	9.0	5,540,000	92	1.08	7.77
46	10.8 11.4	6,020,000 6,400,000	104 108	1.11 1.10	8.02 7.98
47	9.2 9.4	5,500,000 5,612,000	94 95	1.11 1.10	7.95 7.89
48	9.6	5,640,000	94	1.11	7.93
55	10.5	5,900,000	100	1.10	7.96

The viscosity values shown in Table XV were found to be between 9.0 and 12.4 - which represent definite increases above normal - and to be associated with raised erythrocyte counts ranging from 5,500,000 to 7,000,000 per c.mm., and with haemoglobin readings from 92 to 116 per cent. Regarding the size of the erythrocytes, it was found that eight of these cases were included in Table VIII, as having volume indices of 1.09 or over, and significantly increased mean diameter values above the

normal average. The exception was Case 45, a patient with syphilitic aortic regurgitation and co-existing chronic bronchitis and emphysema, who showed only probable increases above normal in the size of the red cells (being therefore included in Table X), but who nevertheless had a raised blood viscosity of 9.0.

It appeared that a fairly close correspondence existed between the high viscosity values in these nine cases, and the increase above normal in number and size of the red corpuscles.

The viscosity readings in the remaining eleven cases with viscosities over 6.0 are shown in Table XVI, which also includes red cell counts, haemoglobin percentages, volume indices and average diameters of red cells.

TABLE XVI

Case No.	Viscosity (Water = 1.0)	Red Cells per c.mm.	Haemo-globin %	Volume Index	Diameter in μ
33	7.0	4,730,000	74	1.05	7.64
36	7.8	4,800,000	80	1.06	7.75
	8.0	4,864,000	80	1.08	7.78
	8.6	5,128,000	82	1.07	7.78
37	7.9	4,840,000	75	1.07	7.79
39	*7.3	4,496,000	74	1.08	7.80
40	6.7	4,496,000	68	1.02	7.60
	7.0	4,560,000	70	1.03	7.58
42	8.0	5,600,000	90	1.02	7.50
43	8.6	5,280,000	88	1.08	7.80
49	8.2	5,240,000	88	1.06	7.76
51	8.4	5,200,000	85	1.09	7.85
53	7.5	4,484,000	70	1.07	7.75
56	7.7	5,400,000	84	1.00	7.52

* This reading was taken after a 24 hours' diuresis up to 100 oz. with considerable diminution in oedema.

The viscosity readings in Table XVI, although on the whole much lower than those in Table XV, were nevertheless still somewhat raised above the normal limit, having ranged from 6.7 to 8.6. Most of the red cell counts in these cases were below 5,000,000 per c.mm., and the few that were over this figure, were not raised to the same extent as those in Table XV, with the exception of Cases 42 and 56, who had counts of 5,600,000 and 5,400,000 respectively.

The haemoglobin percentages were also lower than those in Table XV.

With regard to the size of the cells in these 11 cases, as compared with the normal averages, one case (No. 51) had a significantly increased diameter value of 7.85μ and a corresponding volume index of 1.09; six cases (Nos. 36, 37, 39, 43, 49 and 53) had probable increases in mean diameter value - two with an almost significantly raised reading of 7.80μ - and volume indices ranging from 1.06 to 1.08; and the remaining four cases (Nos. 33, 40, 42 and 56), had red cells which, according to the standard of differences, showed no deviation in size from the normal.

In seven of these 11 cases shown in Table XVI, it appeared that the hyperviscosity could in part be related to a significant or probable increase above normal in size of the red cells, and possibly also in a few cases to slight increase in their number, although the evidence of this relationship was much less striking than in the cases comprising Table XV.

In the remaining four cases of Table XVI, however, there was

apparently no evidence, as far as could be obtained by the writer, that the increase in blood viscosity was related to increase in volume or diameter of the corpuscles, while there was only evidence in two cases (Nos. 42 and 56) that the tendency to hyperviscosity was related to a raised red cell count over 5,000,000.

Of the three cases with viscosity values between 4 and 5, one was Case 34, admitted in extremis with auricular fibrillation and general anasarca, and the other two were Cases 52 and 54, of infective endocarditis, and cardiac failure.

The case with a viscosity reading under 4 was the remaining case (No. 50) of infective endocarditis.

Returning to Case 34, it was observed that although the volume index and average diameter of the red corpuscles were raised above normal, the viscosity reading of 5.0 was much lower than that of any of the other cases of Tables XV and XVI, exhibiting such corpuscular enlargement. It was noted, however, that a diminution was present in the oedematous stage, in both the red cell count and haemoglobin percentage, the readings being 4,520,000 and 73 per cent., respectively. This patient died shortly after admission, so that no further observations could be made.

Gross oedema was also present in Cases 39 and 51, and it was found that in both cases the blood viscosity was relatively lowered in the stage of anasarca, being 4.9 and 5.5 respectively, in association with a lowered erythrocyte count and haemoglobin percentage. The diminution in viscosity with increase in oedema is apparently well illustrated in Case 51, when the above-mentioned

reading of 5.5 is compared with that of 8.4 at the previous examination when oedema was only moderate. In each of these two cases, it was found that the viscosity rose with subsidence of oedema following diuresis - in Case 39 to 7.3, and in Case 51 to 7.5 - and that this rise was associated with the coincident increase in count and haemoglobin percentage already referred to.

In another case (No. 47) with marked oedema (although not amounting to anasarca), the viscosity of the blood was raised above the normal limit in the oedematous stage, the reading being 9.2. This case, however, exhibited a rise in red cell count above 5,000,000 per c.mm. in the capillary blood, as previously noted, besides an increase above normal in the size of the cells.

It would appear that viscosity of the blood is relatively lowered in the stage of marked oedema, only when the latter is associated with relative reduction in red cell count and haemoglobin percentage - in other words, when, as will be discussed later, a condition of hydraemia is presumably present. In such cases, the blood viscosity is raised with diuresis and subsidence of oedema, in association with the increase in haemoglobin and red cells. In such cases also, parallelism apparently exists in the oedematous stage between viscosity, erythrocyte count and haemoglobin percentage, but not between viscosity and size of red cells, the latter being frequently larger than normal in volume and diameter, in conjunction with the relatively lowered viscosity. The size of the cells can thus have little or no

influence on blood viscosity when hydraemia is present.

It was found that improvement in clinical condition, with re-establishment of "compensation", which occurred in eight of the patients in whom viscosities were determined, was associated with a fall in blood viscosity - in the majority of cases to values within normal limits - together with a reduction in red cell count, haemoglobin percentage, and volume and diameter of the erythrocytes. This may be taken as further evidence that some part in the hyperviscosity of congestive heart failure has been played by increase in number and size of the red blood corpuscles.

Excluding for the moment Case 39, who will be described separately, Table XVII illustrates the reduction in blood viscosity on clinical improvement in the remaining seven cases, two of which (Cases 43 and 49) are taken from Table XVI :-

T A B L E XVII

Showing Fall in Viscosity in seven cases with clinical improvement, with coincident reduction in number and size of the erythrocytes and in haemoglobin percentage.

Case No.	Condition	Viscosity (Water = 1.0)	Red Cells per c.mm.	Haemo-globin %	Volume Index	Diam. in μ
35	(Serious	11.6	6,204,000	105	1.13	8.08
	(Improved	6.5	5,372,000	96	1.00	7.56
41	(Serious	11.4	6,300,000	106	1.11	7.96
	(Improved	6.4	5,420,000	98	0.96	7.45
43	(Serious	8.6	5,280,000	88	1.08	7.80
	(Improved	5.4	4,700,000	82	1.00	7.44
47	(Serious	9.2	5,500,000	94	1.11	7.95
	(Improved	5.6	4,800,000	86	0.98	7.52
48	(Serious	9.6	5,640,000	94	1.11	7.93
	(Improved	5.5	5,000,000	88	1.00	7.52
49	(F.Serious	8.2	5,240,000	88	1.06	7.76
	(Improved	5.1	4,692,000	82	0.98	7.49
55	(Serious	10.4	5,900,000	100	1.10	7.96
	(Improved	6.3	5,240,000	94	1.01	7.62

Regarding Case 39, the increase in viscosity occurring with subsidence of oedema following diuresis (which also occurred in Case 51), is no doubt associated with the relative increase in red cells and haemoglobin, that has been noted to occur under such conditions. In the former patient, while no observations were made after 2.9.29 (that is, during his first stay in hospital), it was nevertheless observed during his second stay in hospital, that following the increase in viscosity with diuresis and diminution in oedema, a fall in viscosity to within normal limits, occurred with further clinical improvement, associated with coincident slight reduction in the number of red cells, and further decrease in their size.

It was found that oxygen caused a slight but consistent reduction in blood viscosity in the four patients with severe congestive heart failure, in whom the effects of oxygen were studied.

Table XVIII illustrates this reduction in viscosity with the administration of oxygen, and the coincident slight reduction in number and volume and diameter of the cells, and the haemoglobin percentage :-

T A B L E XVIII

Reduction in Blood Viscosity following inhalation of oxygen.

Case No.	Viscosity (Water = 1.0)	Red Cells per c.mm.	Haemoglobin %	Volume Index	Diam. in μ	Remarks
35	11.6	6,204,000	105	1.13	8.08	Before oxygen
	9.6	5,800,000	100	1.08	7.82	After oxygen
41	11.4	6,300,000	106	1.11	7.96	Before oxygen
	9.6	5,900,000	102	1.07	7.71	After oxygen
44	10.4	5,700,000	96	1.12	7.98	Before oxygen
	9.0	5,420,000	92	1.08	7.78	After oxygen
46	11.4	6,400,000	108	1.10	7.98	Before oxygen
	9.8	5,872,000	102	1.07	7.76	After oxygen

The findings in this section dealing with viscosity of the blood may be summarised as follows :-

1. Of the 24 cases of congestive heart failure shown in Table VII, in which blood viscosity estimations were included, it was found that 20 cases (83 per cent.) give readings over 6.0, the reading taken to represent the upper limit of the

of 4.0 to 6.0,
normal range,/ in which range is included the average value for the normal subjects (5.32) and that for the compensated cases (5.60). The viscosity values in these 20 cases ranged from 6.7 to 12.4.

2. In nine of these cases, a relationship appeared to exist, as shown in Table XV, between the hyperviscosity and the increase above normal in the number of erythrocytes, and in their individual volume and diameter. High viscosity values of from 9.0 to 12.4 were present in these 9 patients, who exhibited raised erythrocyte counts ranging from 5,500,000 to 7,000,000 per c.mm. (and haemoglobin readings from 92 to 116 per cent.), and significant increases in the size of individual erythrocytes above normal in 8 of the cases, and a probable increase above normal in the remaining case.

3. (a) In the remaining eleven cases with blood viscosity values over 6.0, these values ranged from 6.7 to 8.6, (as seen in Table XVI) and were, therefore, relatively lower than those in Table XV. Most of the erythrocyte counts in these cases were below 5,000,000 per c.mm., and the few that were above this figure were, with two exceptions - where the counts were 5,600,000 and 5,400,000 - not raised to the same extent as those in Table XV. The haemoglobin percentages were also lower than those of Table XV.

(b) One of these cases, however, had red cells significantly increased in diameter above normal, according to the standard of differences, with a corresponding volume index of 1.09,

while another six cases had red cells with probable increases in diameter above normal, and volume indices ranging from 1.06 to 1.08. The red corpuscles in the remaining four cases could apparently be disregarded as showing any deviation in size from the normal, according to the standard of differences.

(c) In seven of these eleven cases, it appeared that the increase in blood viscosity was possibly related in part to a significant or probable increase above normal in size of the individual corpuscles, and in a few cases also to a slight increase in their number, although this apparent relationship was much less marked than in the cases shown in Table XV. In the remaining four cases, there was no evidence, according to the standard of differences, that the hyperviscosity was related to corpuscular enlargement above normal, while there was only evidence in two cases that it was related to increase in the red corpuscle count above normal. In these two cases, however, the viscosity values were relatively higher than in the other two cases of the last-mentioned group of four cases.

4. Improvement in general clinical condition was accompanied, as illustrated in Table XVII, by reduction in blood viscosity (with generally a return to values within normal limits), together with the coincident reduction in red cell count, haemoglobin percentage, volume index and average diameter of the erythrocytes, already noted in previous sections of the analysis of the results. This supports, to

some extent, the apparent parallelism between the increased viscosity of the blood in congestive heart failure, and the increase in size and number of the erythrocytes.

5. Inhalation of oxygen was observed to bring about a reduction in the viscosity of the blood, together with the coincident slight reduction in number and volume and diameter of the corpuscles, and in haemoglobin percentage, previously noted.

6. The viscosity readings in the cases of congestive heart failure where infective endocarditis was superimposed on chronic valvular disease, were below normal limits (i.e. below 4.0) in one case, and barely within the normal range, at its lower limit, in the remaining two cases.

7. (a) In three cases with general anasarca, a relatively lowered viscosity was obtained, in association with a lowered red cell count and haemoglobin percentage. The individual red cells in these cases gave high values for volume index and significantly increased diameter values above normal, so that in these cases, where gross oedema was present, the viscosity of the blood apparently stood in direct ratio to the number of erythrocytes and the haemoglobin percentage but not to the size of the cells. Two of the above mentioned three cases exhibited a subsequent rise in viscosity with diminution in oedema following diuresis, associated with an increase in count and haemoglobin percentage, but one of them also showed that when further

clinical improvement occurred, the viscosity of the blood fell, in association with a reduction in red cell count and haemoglobin percentage.

(b) In another case with marked oedema, which did not, however, amount to general anasarca, the blood viscosity was raised in the oedematous stage. The latter stage was, however, in this case, associated with an increased erythrocyte count above 5,000,000, as compared with the relatively diminished count in the three cases above mentioned.

TABLE XIX

CASE E.W. OBSERVATIONS IN A CASE OF RHEUMATIC CARDITIS, WITH MITRAL STENOSIS AND REGURGITATION, SHOWING SEVERE CONGESTIVE HEART FAILURE, WITH EXACERBATIONS AND REMISSIONS.

Date	Condition and Clinical Notes	Red Cells per c.mm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ
6.5.29	Girl aged 10 years. Rheumatic fever 10 months previously. Admitted 3.5.29 with severe congestive heart failure. Clinical condition on 6.5.29 :- Malar flush, pulsation of cervical veins; dyspnoeic, orthopnoeic, cyanosed; heart enlarged, with systolic and diastolic murmurs at apex, and tricuspid systolic murmur; numerous fine crepitations at bases of both lungs, persistent cough; enlarged, tender liver, slight ascites; oedema of legs, thighs, and lumbar back; urine: S.G. 1026, albumin present. Temperature 98.0° F. Pulse 140, regular. Respirations 28. Urinary output for past 24 hours = 24 oz.	4,048,000	68	45	1.11	0.84	7.98
9.5.29	Condition still serious, but oedema less; urinary output = 39 oz.	4,400,000	76	48	1.09	0.86	7.84
14.5.29	General Anasarca present. Urinary output for past 24 hours = 20 oz.	3,840,000	65	42	1.09	0.84	7.90
18.5.29	Slightly improved. Oedema much less; dyspnoea and cyanosis less. Pulse 100. Respirations 24. Urinary output has increased; e.g. for past 24 hours it was 50 oz.	4,700,000	80	50	1.06	0.85	7.70
22.5.29	Condition poor. More dyspnoea and cyanosis; acute bronchitis present, also marked congestion both lung bases; liver enlarged and tender; increase in oedema of feet and legs. Temperature 100.4° F. Pulse 140. Respirations 36. Urinary output = 34 oz.	5,240,000	86	57	1.09	0.82	7.85
do.	..... After inhalation of oxygen, less cyanosis and dyspnoea.	4,816,000	82	51	1.05	0.85	7.64
25.5.29	Condition improved. Dyspnoea slight; slight oedema of ankles only; liver smaller, no ascites. Pulse 108. Respirations 24. Urinary output = 42 oz.	4,680,000	80	48	1.02	0.85	7.50
29.5.29	More dyspnoea and cyanosis; well-marked signs of pulmonary congestion. Liver increased in size and tender. Oedema of feet and legs, slight ascites. Temperature 99° F. Pulse 120. Respirations 30. Albumin in urine.....	5,200,000	84	56	1.08	0.80	7.80
do.	..... After oxygen, less dyspnoea and cyanosis.....	4,800,000	81	50	1.04	0.84	7.60
14.6.29	Generally much improved. No dyspnoea at rest, cyanosis very slight; liver only slightly enlarged, not tender; oedema nil; lung bases clear. Pulse 90. Respirations 22.....	4,648,000	80	46	0.99	0.86	7.46
25.6.29	Condition very poor. Fine moist râles at lung bases with slightly impaired percussion; oedema present again in feet and legs; liver increased in size. Severe dyspnoea, more marked cyanosis. Temperature 98.8° Pulse 120. Respirations 30.....	5,180,000	85	58	1.11	0.82	7.90
do.	..... After oxygen, less dyspnoea and cyanosis.....	4,852,000	82	52	1.07	0.84	7.68
18.7.29	Condition greatly improved and practically no evidence of heart failure. No dyspnoea; cyanotic tinge of lips only; lungs clear; liver only slightly enlarged, and not tender. No oedema. Urine: No albumin, S.G.1016. Pulse-rate 88. Respirations 20.	4,600,000	80	46	1.00	0.87	7.42

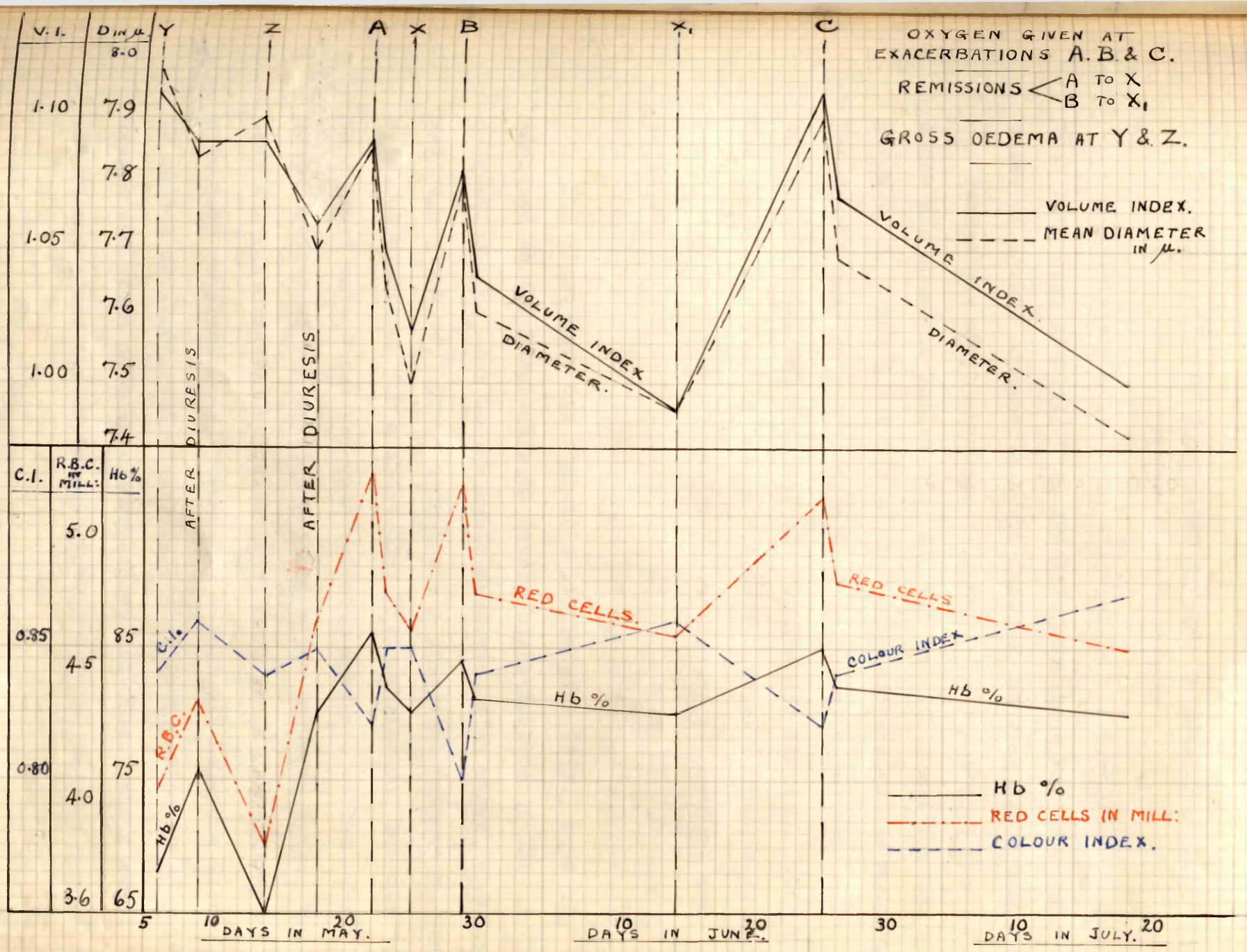


FIG. I. CASE E.W. GRAPHIC REPRESENTATION OF DATA IN TABLE XIX, IN A CASE OF CONGESTIVE HEART FAILURE WITH EXACERBATIONS AND REMISSIONS.

DESCRIPTION OF FOUR CASES STUDIED IN GREATER DETAIL

As previously stated, in addition to the foregoing 36 cases that have been studied, frequent determinations were made on four cases of severe congestive heart failure, showing exacerbations and remissions of the cardiac failure. The results in these four cases are shown in Tables XIX, XX, XXI and XXII, and charted in Figures 1, 2, 3 and 4. A further set of observations was made on the fourth case on readmission to Hospital with recurrence of congestive heart failure, and the results are shown in Table XXIII. Two cases were studied before viscosity determinations were undertaken, and in the other two cases, viscosity estimations are included.

The first case was that of a little girl (E.W.) aged 10, admitted to the Hospital with severe heart failure of the congestive type, due to rheumatic carditis, with mitral stenosis and regurgitation. Gross oedema was a prominent feature of the clinical condition for a short time after admission, but was soon to a great extent removed with suitable treatment. The three exacerbations of the cardiac failure which occurred during the time she was observed by the writer, were associated mainly with pulmonary complications, although a coincident moderate increase in oedema occurred, and an increase also in hepatic enlargement. Oxygen was given at each exacerbation, and observations made before and after its administration.

The results in this case are shown in Table XIX (which relates the blood findings to the clinical condition) and charted in Figure 1.

The principal points observed in this case were as follows :-

1. A close correspondence existed between volume index and mean red cell diameter, their curves in Figure 1, being practically parallel.

2. Observations made in the stage of advanced failure associated with gross oedema (as on 6.5.29 and 14.5.29), revealed a relative reduction in erythrocyte count and haemoglobin percentage. The values for volume index and mean diameter of the corpuscles in this stage, were above normal, although not materially different from those at subsequent exacerbations of the heart failure when oedema was not such a pronounced clinical feature.

3. On 18.5.29, when considerable diminution in the oedema mentioned under (2) had occurred, following treatment with diuretics, an increase was found to have taken place in red cell count and haemoglobin percentage, together with a slight diminution in volume and diameter of the individual corpuscles. Less marked changes, but nevertheless of a similar character, were observed on 9.5.29, following some diminution in oedema.

4. On three occasions after 18.5.29, when exacerbations of the cardiac failure occurred and were associated with well-marked pulmonary complications, the volume index and

mean diameter of the erythrocytes gave values raised above the normal averages, with diameters in two of the exacerbations indicating a significant enlargement of the corpuscles above normal, and in the third one, an almost significant enlargement above normal. An increase was also observed on each occasion, in red cell count and haemoglobin percentage, relatively more marked in the former than in the latter, so that each exacerbation was characterised by a slight diminution in the value for colour index. The average red cell count for the three exacerbations of the cardiac failure, was found to be 5,200,000 per c.mm., while the average haemoglobin value was 85 per cent.

5. The effects of oxygen administered at the time of the exacerbations described under (4) for the increased cyanosis and dyspnoea, were found to be a slight but consistent diminution in volume index and mean diameter of the erythrocytes, together with a coincident slight reduction in red cell count and haemoglobin percentage. These effects are illustrated in Figure 1, at A, B and C.

6. More complete remission of the circulatory symptoms following the slight clinical improvement after oxygen, was associated with further reduction in red cells, and to a less extent in haemoglobin, and also a further diminution in volume index and mean diameter of the cells to normal values.

7. The relationship observed in Figure 1, between the curves for volume index, mean diameter, and colour index,

showed that the increase in size of the corpuscles at exacerbations A, B, and C, was not accompanied by a corresponding increase in their average haemoglobin content, the latter, in fact, showing on these occasions, a tendency to slight reduction in value.

This little girl maintained her improvement for some time after the date of the last observation, but later developed a recurrence of the heart failure, and died.

I was away at the time, so that no further observations were made.

TABLE XX

CASE W.O'C. OBSERVATIONS IN A CASE OF MITRAL STENOSIS AND REGURGITATION, SHOWING SEVERE CONGESTIVE HEART FAILURE.

Date	Condition and Clinical Notes	Red Cells per c.mm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ
8.5.29	Male, aged 25. No history of rheumatic fever, but one of growing pains when a boy. Increasing breathlessness for four months prior to admission. Admitted 8.5.29, with advanced congestive heart failure. Face flushed, engorgement and pulsation of cervical veins; cyanosed and slightly icteric, orthopnoeic and dyspnoeic; numerous moist râles at bases of lungs with slight dulness; moderate oedema of feet and legs; liver enlarged, pulsating and tender. Heart enlarged, with signs of mitral stenosis and regurgitation; and tricuspid regurgitation. Temperature 98.8°. Pulse 120, regular. Respirations 28. Urine: S.G.1026, albumin present, and occasional hyaline casts	6,108,000	100	68	1.11	0.81	7.96
16.5.29	Improvement in condition. Dyspnoea and cyanosis less; oedema of feet only; liver slightly diminished in size.....	5,580,000	95	59	1.05	0.85	7.71
21.5.29	Improvement maintained. Fair condition. Pulse rate 94. Respirations 22..	5,340,000	92	57	1.06	0.86	7.68
6.6.29	Condition bad. Pronounced dyspnoea and orthopnoea; marked cyanosis; liver greatly enlarged; ascites present; increase in oedema, now in legs and thighs, and slightly in lumbar back. Right hydrothorax; congestion and oedema at lung bases. Pulse rate 126. Respirations 30. Temperature 99° F.....	5,816,000	97	64	1.10	0.83	7.89
10.6.29	Slight improvement in condition. Dyspnoea relieved after paracentesis performed for hydrothorax and oxygen inhalations. Urinary output increased after 0.75 cc. novasural, in addition to digitalis therapy ...	5,500,000	93	58	1.05	0.84	7.67
13.6.29	Fair condition. Moderately dyspnoeic and cyanosed. Lungs still congested; oedema of feet and legs; liver as before, slight ascites; urine: albumin present, S.G. 1022. Pulse rate 118, regular. Respirations 26.....	5,420,000	92	57	1.05	0.85	7.70

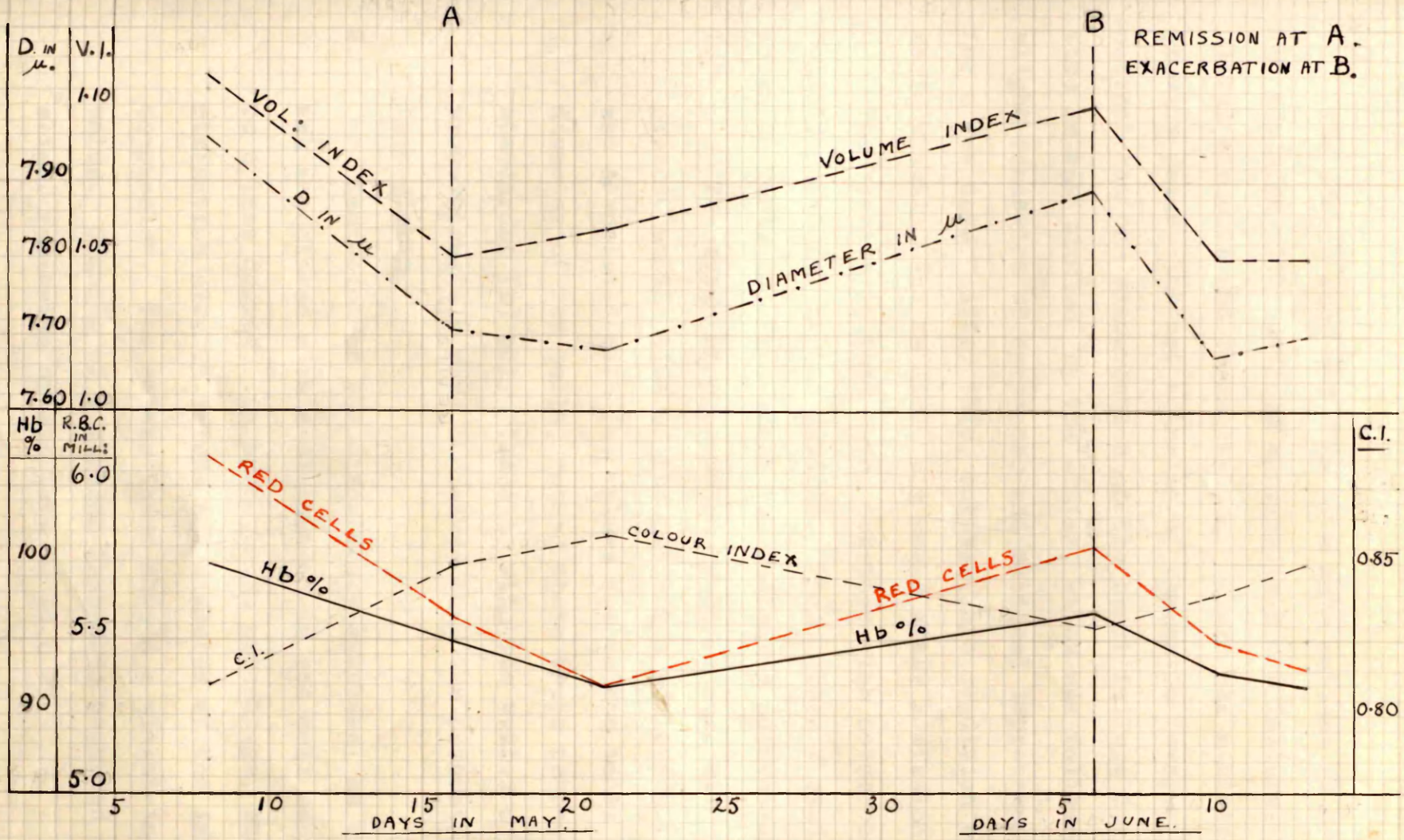


FIG. 2. CASE W. O'C. GRAPHIC REPRESENTATION OF DATA IN TABLE XX, RELATING TO A CASE OF SEVERE CONGESTIVE HEART FAILURE, WITH EXACERBATION AND REMISSION OF CIRCULATORY SYMPTOMS.

The second case was that of a male patient (W.O'C.), aged 25, admitted with advanced congestive heart failure, due to mitral stenosis and regurgitation. There was a history of growing pains, but not actually of rheumatic fever. This patient had one exacerbation of the heart failure during the time he was studied by the writer, which was followed by a slight remission of symptoms, and clinical improvement maintained for a few days. After this, however, his condition became serious again, and he died, six weeks after admission.

The results in this case, together with notes on clinical condition (as far as the patient has been studied) are shown in Table XX, from which the following points emerged :-

1. The stage of pronounced heart failure with congestion, present at the time of the patient's admission to hospital, was associated with (a) values for volume index and average diameter of red cells, raised above their respective normal standards; (b) polycythaemia, with the number of red cells proportionately more increased than the percentage of haemoglobin.

2. Remission of the circulatory symptoms, as on 16.5.29, was associated with a diminution in red cell count, and - to a less degree - in haemoglobin percentage, and a slight diminution also in volume and diameter of the individual corpuscles. The colour index showed a slight increase in value. Changes of a similar character occurred with the slight remission of symptoms on 10.6.29.

3. Exacerbation of the heart failure on 6.6.29, was associated with increase in volume index and mean diameter of the red cells (the diameter value indicating, according to the standard of differences, a significant increase in size of the corpuscles above their average normal size), and an increase in red cell count and - to a less extent - in haemoglobin percentage. The enlargement of the erythrocytes was not accompanied, under these conditions, by a corresponding increase in the haemoglobin content of the corpuscles, the colour index, in fact, tending to show a slight diminution in value.

A graphic representation of the data given in Table XX, relating to volume and diameter of red cells, red cell count, haemoglobin percentage and colour index, is shown in Figure 2.

TABLE XXI

CASE J.G. OBSERVATIONS IN A CASE OF ADHERENT PERICARDIUM, MITRAL STENOSIS AND REGURGITATION, SHOWING SEVERE CONGESTIVE HEART FAILURE WITH EXACERBATIONS AND REMISSIONS.

Date	Condition and Clinical Notes	Red Cells per c.mm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ	Viscosity (Water = 1.0)
2.7.29	Male, aged 17. History of three attacks of rheumatic fever (once in 1919 and twice in 1927). Increasing breathlessness and swelling of legs and abdomen for some weeks before admission. Admitted 1.7.29, with severe congestive heart failure. Face flushed, pulsation of veins in neck; orthopnoeic, dyspnoeic and cyanosed; numerous fine crepitations at bases of lungs, and slightly impaired percussion, bad cough; heart greatly enlarged, signs of adherent pericardium, mitral stenosis and regurgitation and tricuspid regurgitation; liver much enlarged, tender, ascites present; oedema of legs and thighs. Urine: S.G. 1024, albumin present, no casts seen. Temperature 99.0° F. Pulse 120, regular. Respirations 28.....	5,910,000	96	65	1.10	0.81	7.98	9.6
11.7.29	Condition somewhat improved. Less dyspnoea and cyanosis, lung bases clearer; oedema of legs only.....	5,300,000	92	56	1.05	0.86	7.70	7.4
14.7.29	Not so well. More dyspnoea and cyanosis, fine moist râles at bases of lungs. Ascites still present; oedema of legs, and slight pitting of thighs.....	5,620,000	94	61	1.08	0.83	7.86	8.5
20.7.29	Condition practically unchanged.....	5,700,000	94	61	1.07	0.82	7.88	8.4
2.8.29	Improvement in condition. Slight dyspnoea and cyanosis; oedema of feet only, liver still enlarged but not tender. Lungs clearer. Trace of albumin in urine. Pulse rate 90. Respirations 22.....	5,200,000	90	53	1.02	0.86	7.58	6.5
19.8.29	Increase in dyspnoea and cyanosis. Congestion and oedema both lung bases. Temperature 99° F. Pulse 110. Respirations 28.	5,800,000	95	63	1.09	0.82	7.90	8.6
do.	..... After oxygen administration	5,432,000	92	57	1.05	0.84	7.69	7.4
7.9.29	General condition much improved. No orthopnoea or dyspnoea, lungs clear. Slight cyanotic tinge of lips, liver slightly enlarged, but not tender. No oedema, no ascites. No albumin in urine. (Urinary output = 50 oz.); Pulse rate 86, Respirations 20.....	5,040,000	89	50	0.99	0.88	7.50	6.0

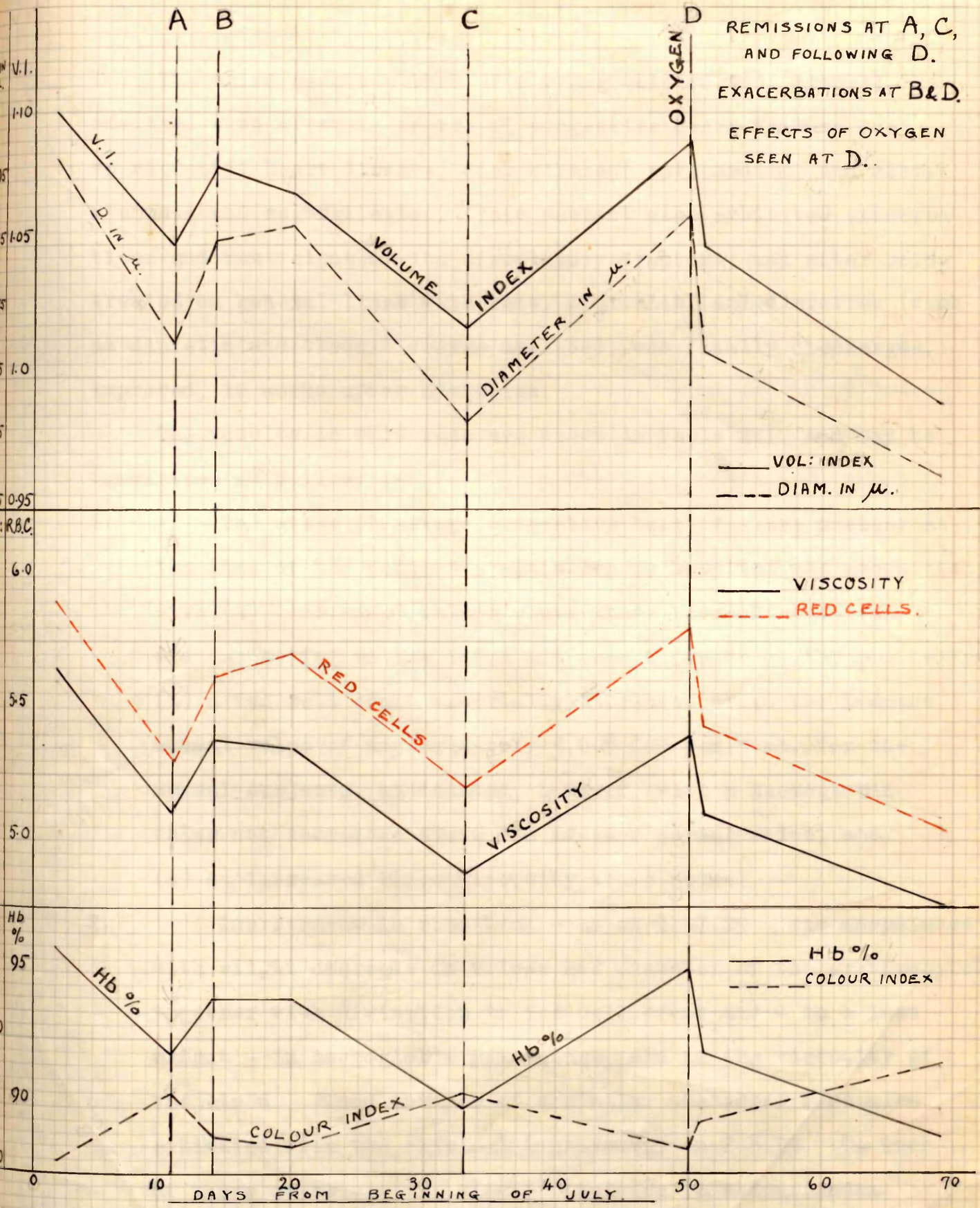


FIG. 3. CASE J. G. GRAPHIC REPRESENTATION OF DATA IN TABLE XXI. ILLUSTRATES RELATIONSHIP BETWEEN VISCOSITY OF THE BLOOD AND SIZE AND NUMBER OF ERYTHROCYTES IN CONGESTIVE HEART FAILURE.

The third case was that of a young male (J.G.), aged 17, admitted with a severe degree of congestive heart failure due to rheumatic heart disease, with adherent pericardium, and mitral stenosis and regurgitation. This patient also exhibited exacerbations and remissions of the circulatory symptoms, and after being treated on general lines with rest, digitalis, and diuretics (such as diuretin and theocin sodium acetate), was finally discharged, improved, 12 weeks after admission.

The results in this case are shown in Table XXI, and may be summarised as follows :-

1. The stage of severe congestive heart failure present at the time of the patient's admission to hospital was associated with (a) increased values above their respective normal standards, for volume index and mean diameter of the red cells; (b) a red cell count materially increased above the average normal value of approximately 5,000,000 per c.mm. for the normal subjects, associated, however, with a haemoglobin value not increased above the average normal value, and (c) an increased blood viscosity above normal.

2. Improvement in condition - as on 11.7.29 - was associated with slight decrease in volume and diameter of the erythrocytes, together with diminution in red cell count and - to a less extent - in haemoglobin percentage, and in the viscosity of the blood. Blood changes of a similar character were also exhibited with the clinical improvement on 2.8.29. On each of these occasions, a slight increase in colour index value was observed.

3. In the stage of exacerbation of the circulatory symptoms

as on 14.7.29 and 19.8.29 - the blood, as compared with the preceding stage of clinical improvement, exhibited (a) increase in volume index and mean diameter of the red cells; (b) increase in the number of red cells, and - to a less extent - in haemoglobin percentage; (c) increase in blood viscosity, and (d) slight decrease in colour index.

4. The effects of oxygen administration on 19.8.29, were a slight diminution in red cell count, haemoglobin percentage, volume and diameter of the red cells, and blood viscosity.

5. In the stage of marked improvement, present at the date of the last observation - 7.9.29 - when there was practically no evidence of heart failure, the peripheral blood, as compared with what was observed at the time of the patient's admission to hospital, showed a distinct reduction in red cell count, and - to a less extent - in haemoglobin percentage, and a diminution in volume and diameter of the cells and in blood viscosity. The colour index, however, exhibited a slight increase in value. In this stage of improvement, the erythrocyte count was at the normal standard, and the volume index, average cell diameter, and blood viscosity gave normal values, although the viscosity was at the upper limit of the normal range.

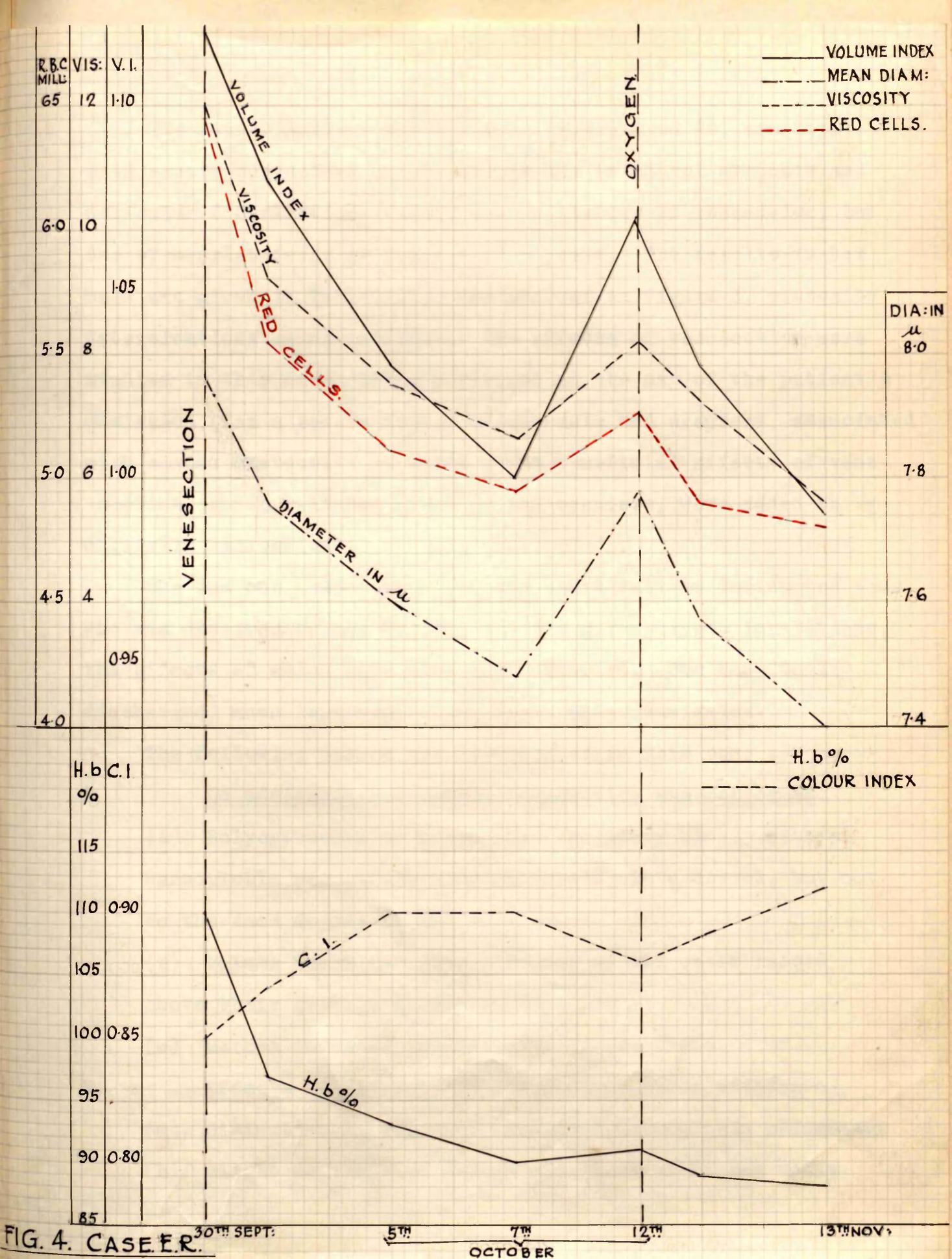
The data given in Table XXI are charted in Figure 3, on which the close relationship between the viscosity of the blood and the number and size of the corpuscles is well illustrated. The absence

of a direct ratio between the size of the red cells and their individual haemoglobin content is also illustrated, a tendency to an inverse ratio being in fact present, increase in volume and diameter of the corpuscles being associated with a slight decrease in colour index and vice versa.

TABLE XXII

CASE E.R. OBSERVATIONS IN A CASE OF MITRAL STENOSIS AND AURICULAR FIBRILLATION, SHOWING SEVERE CONGESTIVE HEART FAILURE.

Date	Condition and Clinical Notes	Red Cells per c.mm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ	Viscosity (Water = 1)
30.9.29	Female, aged 28. No history of rheumatic fever, but scarlet fever at 7 years, and bronchitis and congestion of lungs in 1928. History of heart "jumping" for five years and increasing shortness of breath, swelling of ankles and abdomen, exhaustion and cough for about three weeks before admission. Admitted 29.9.29, with pronounced congestive heart failure. High coloured, marked distension and pulsation of cervical veins, extremely cyanosed with icteroid tinge to conjunctivae; orthopnoeic and extremely dyspnoeic; fine moist râles and some dulness at bases of lungs; persistent cough. Oedema of feet and legs; liver greatly enlarged and tender, slight ascites present; heart enlarged, signs of mitral regurgitation and stenosis, and tricuspid regurgitation; auricular fibrillation, ventricular rate 140, radial pulse 100. Temperature 99° F. Respirations 34. Urine: S.G. 1028, albumin present and occasional hyaline casts.....	6,420,000	110	72	1.12	0.85	7.96	12.0
do.	..... After venesection. Dyspnoea relieved, cyanosis less	5,600,000	97	61	1.08	0.87	7.76	9.2
5.10.29	Improvement maintained. Ventricular rate 110, radial pulse 80...	5,120,000	93	53	1.03	0.90	7.60	7.5
8.10.29	Condition much improved. No orthopnoea, slight dyspnoea and cyanosis, lung bases practically clear, cough better; slight oedema of ankles; liver much diminished in size, not tender. Respirations 20. Ventricular rate 80, no pulse deficit. Urine: albumin, a trace.....	4,960,000	90	50	1.00	0.90	7.48	6.6
12.10.29	Condition serious again. More dyspnoeic and cyanosed; marked signs of pulmonary congestion, some bronchitis also present; liver increased in size and tender; oedema of feet and legs. More albumin in urine. Temperature 99.4° F. Ventricular rate 120, radial pulse 90.....	5,280,000	92	57	1.07	0.87	7.78	8.2
do.	..... After oxygen. Less dyspnoea and cyanosis	4,950,000	89	51	1.03	0.89	7.58	7.2
13.11.29	Condition greatly improved, practically no evidence of heart failure. No dyspnoea, slight cyanotic appearance of lips only; lung bases clear, liver still palpable, but not tender, no ascites. No oedema. No albumin in urine, S.G. 1018. Respirations 18. Ventricular rate 70, no pulse deficit.....	4,824,000	88	48	0.99	0.91	7.40	5.8


R.B.C MILL:
VIS:
V.I.
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12
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0·95
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VOLUME INDEX
VISCOSITY
RED CELLS.
DIAMETER IN μ
VENESECTION
OXYGEN
VOLUME INDEX
MEAN DIAM:
VISCOSITY
RED CELLS.
DIA: IN μ
8·0
7·8
7·6
7·4
H.b %
C.I
115
110
0·90
105
100
0·85
95
90
0·80
85
C.I.
H.b %
H.b %
COLOUR INDEX
30TH SEPT:
5TH
7TH
12TH
13TH NOV:
OCTOBER

FIG. 4. CASE E.R.

The fourth patient was a female (E.R.) aged 28, admitted with severe congestive heart failure due to mitral stenosis and auricular fibrillation. There was no history of rheumatism, but one of scarlet fever at the age of 9 years. The results in her case are given in Table XXII, and charted in Figure 4, viscosity determinations being included. The effects of venesection were studied in this case, being performed on the day of the patient's admission, for a severe degree of cyanosis and dyspnoea, associated with marked distension of veins. The beneficial effects of venesection, which relieved dyspnoea and cyanosis, were added to by digitalis medication.

She had one exacerbation of the heart failure during the time she was observed by the writer, and was given oxygen inhalations, the effects of which have also been recorded. She was finally discharged, much improved, eight weeks after admission.

The following points are illustrated in this case :-

1. <u>On admission and before venesection was performed</u>.

(a) Polycythaemia of peripheral capillary blood, with a haemoglobin percentage also increased above normal, but not to the same degree as the cell count.

(b) Volume index and mean diameter of red cells raised above their average normal values.

(c) Marked increase in viscosity of the blood.

2. <u>Effects of Venesection</u> (18 ozs. of blood withdrawn).

(a) Diminution in red cell count and haemoglobin percentage.

(b) Slight decrease in volume and diameter of red cells.

(c) Fall in blood viscosity.

3. As improvement in clinical condition was maintained with digitalis therapy, the count and - to a less extent - the haemoglobin percentage, continued to fall, likewise the volume and diameter of the corpuscles, and the blood viscosity, while the haemoglobin content per corpuscle showed a slight increase.

4. On 12.10.29, when the patient's condition was again serious, there being gross pulmonary congestion and more marked signs of heart failure, the peripheral blood, as compared with the previous stage of improvement mentioned under (3), showed a slight increase in volume and diameter of the red cells, a slight increase in red cell count, and - to a less degree - in haemoglobin percentage (the latter being increased by only 2 per cent.), and an increase also in blood viscosity. The effect of oxygen administration on this date was to cause a slight diminution in cell count, haemoglobin percentage, volume and diameter of the cells, and blood viscosity.

5. A fairly well-marked parallelism was observed in Figure 4, between the curves for viscosity, volume index, mean cell diameter, erythrocyte count, and haemoglobin percentage. The viscosity of the blood was thus apparently in close relationship with the number and size of the red blood cells, a point previously observed and illustrated also in Figure 3.

TABLE XXIII

CASE E.R. FURTHER OBSERVATIONS FOLLOWING READMISSION TO HOSPITAL

Date	Condition and Clinical Notes	Red Cells per c.mm.	Haemoglobin %	Haematocrit Reading	Volume Index	Colour Index	Aver. Diam. in μ	Viscosity (Water = 1.0)
30.12.29	Readmitted to-day, with recurrence of gross congestive heart failure. Orthopnoea, severe dyspnoea, and cyanosis; fine crepitations at bases of both lungs; oedema of legs; liver enlarged, tender, ascites present; heart enlarged, systolic and diastolic murmurs at apex, tricuspid systolic murmur. Auricular fibrillation, ventricular rate 130, radial pulse 100. Temperature 98.6°. Respirations 28. Urine: S.G.1024, albumin present, no casts seen.....	5,500,000	92	60	1.09	0.83	7.88	9.6
4.1.30	Condition worse. Dyspnoea more severe. Heart rate 160 On 5.1.30, right-sided hydrothorax diagnosed, and 500 cc. fluid withdrawn. Intravenous injection of strophanthin (gr. $\frac{1}{200}$) given.	5,636,000	94	63	1.10	0.83	7.86	9.0
6.1.30	Somewhat improved. Dyspnoea less. Heart rate 100; radial pulse 88; oedema less; liver diminished in size.....	5,192,000	90	55	1.05	0.86	7.67	7.6
22.1.30	Condition much improved. Slight dyspnoea and cyanosis; slight oedema of ankles only; ventricular rate 72, no pulse deficit..	4,952,000	88	51	1.02	0.88	7.49	6.2
1.2.30	Condition fairly serious. More dyspnoea, and cyanosis; ventricular rate 120; liver increased in size; moderate oedema of feet and legs.....	5,240,000	90	56	1.07	0.85	7.73	8.0
23.2.30	Considerable improvement. No orthopnoea, or dyspnoea; cyanosis very slight; no oedema; liver palpable, but not tender, no ascites; lungs clear; no albumin in urine. Ventricular rate 68, no pulse deficit. Respirations 18.....	4,880,000	87	49	1.00	0.89	7.45	5.9

This patient (E.R.) was readmitted to hospital on 30.12.29, with recurrence of severe congestive cardiac failure. A few days after admission, she developed a right-sided hydrothorax, which was aspirated for urgent dyspnoea, and at the same time, an intravenous injection of strophanthin gr. $\frac{1}{200}$ was given, as her condition was grave, and an immediate digitalis effect was required.

She improved after this on the usual lines, and was discharged improved on 15.3.30.

The results, together with notes on clinical condition, are given in Table XXIII. It was found that the changes in size, number and haemoglobin content of the erythrocytes, and in blood viscosity, occurring with exacerbation and remission of the circulatory failure, were similar in character to those previously described.

It will be seen that the four cases of congestive heart failure studied with more frequent determinations, have, on the whole, given results similar in character, as far as departures from the average results obtained in normal individuals are concerned, to those obtained in the majority of the 36 cases of cardiac failure studied in Tables VI and VII. In addition, the effects of exacerbation and remission of the circulatory failure, together with those of such special measures as oxygen administration and venesection, have been illustrated.

In an attempt to give a graphic representation of the relation of the sizes of red blood cells in the cases of cardiac

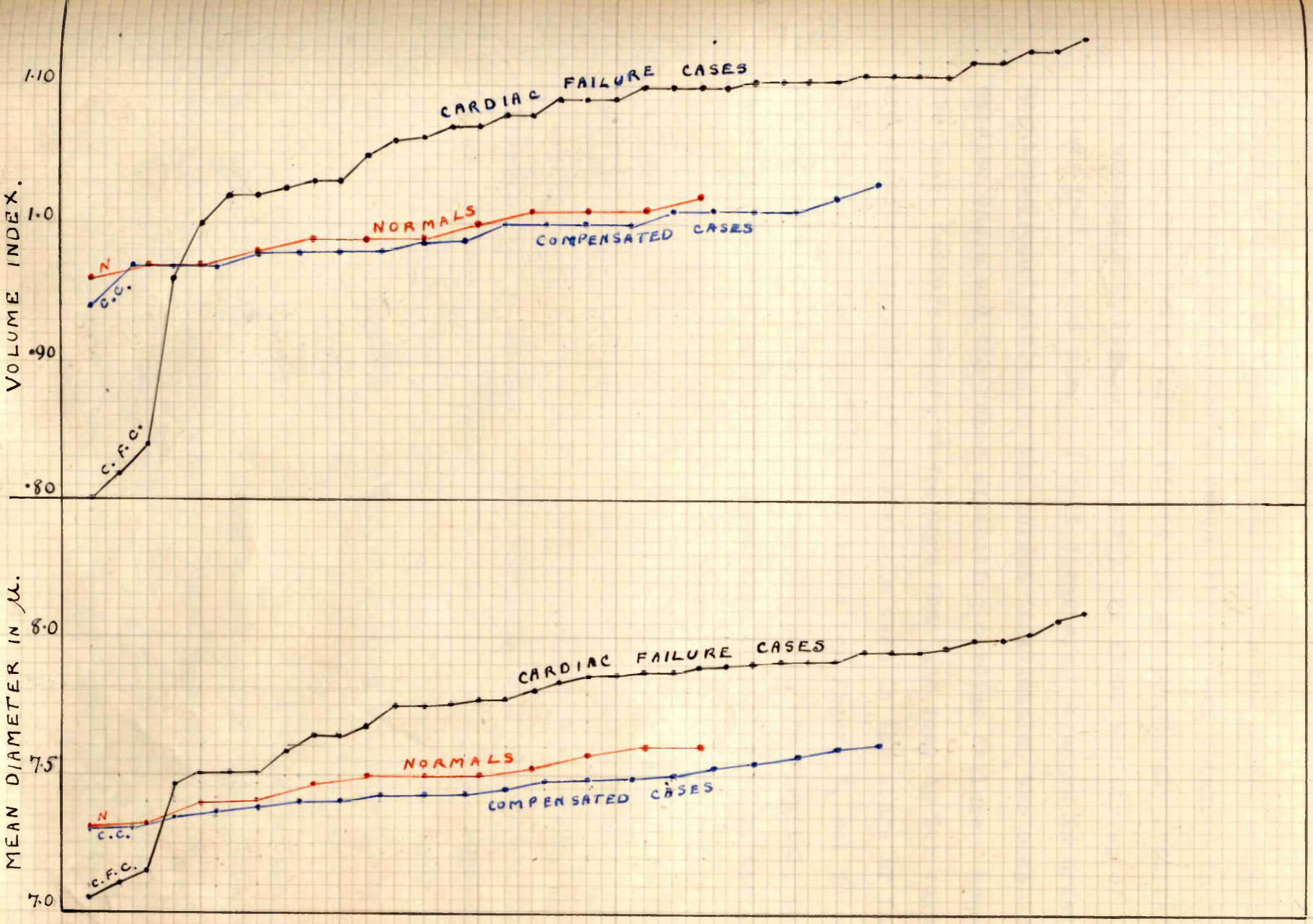
VOLUME INDEX.
1·10
1·0
·90
·80
CARDIAC FAILURE CASES
NORMALS
COMPENSATED CASES
N
C.C.
C.F.C.
MEAN DIAMETER IN μ.
8·0
7·5
7·0
CARDIAC FAILURE CASES
NORMALS
COMPENSATED CASES
N
C.C.
C.F.C.

FIG. 5.

failure studied in this work, to those in the normal subjects and the compensated cardiac cases, the results obtained in the 36 cases comprising Tables VI and VII and previously analysed, are expressed in Figure 5, on which are shown the curves of the volume indices and mean red cell diameters, arranged in order of magnitude, appertaining to the normal individuals, the compensated cardiac cases and the cases exhibiting cardiac failure. Regarding the heart failure cases, where more than one reading for volume and diameter was obtained in a single case in the stage of failure, an average of these readings was taken for Figure 5, but in one of the patients (Case 39) who was readmitted to the Hospital, the readings taken on readmission have also been plotted on the graph.

GENERAL DISCUSSION

This is divided into the following sections :-

I. Volume and Diameter of Red Cells.

II. Number of Red Cells, Haemoglobin Percentage, and Haemoglobin Content of Red Cells.

III. Viscosity of the Blood.

In addition, a brief discussion of the results obtained in the exercise experiments has been added, in so far as they apply to this work.

I. Volume and Diameter of Red Cells.

In a discussion of the results obtained in congestive heart failure, where the erythrocytes of the peripheral capillary blood have in many cases shown a tendency to be increased in volume and diameter above the average values in normal individuals, and in patients with fully compensated heart cases (where the equilibrium of the circulation is still maintained), it is considered that attention should be directed towards disturbances in physiological function occurring with failure of the circulation as a result of the failure on the part of the heart.

In this connection disturbance of the circulation rate with its effect on tissue respiration, would appear to be of importance and merits comment.

A characteristically low circulation rate was found to be present in cardiac failure with venous congestion by Meakins and

Davies (94) and Kininmonth (75) who consider this to be due to inability of the myocardium to maintain a sufficient cardiac output per beat. Such a subnormal circulation rate was apparently characteristic of cardiac failure irrespective of the underlying lesion, as it was found in patients with mitral valvular disease, aortic valvular disease, disturbances of cardiac rhythm, and with myocardial affections where disturbances of rhythm or recognisable endocardial lesions were not present. Meakins and Davies (94) clearly demonstrated that in patients who were free of circulatory symptoms, the circulation rate and systolic output were within normal limits, but that with the development of the signs of cardiac failure the circulation rate or minute blood flow, and the systolic output, rapidly decreased.

Diminished velocity of blood flow was also found by Blumgart and Weiss (13) to be present in cardiac decompensation.

Slowing of the circulation through the tissues will produce a greater lowering of oxygen saturation in the capillary and venous blood, together with an increase in carbon dioxide (95). In other words, a condition of oxygen want and carbon dioxide "acidosis" occurs in the tissues - together with a tendency therein to increased hydrogen ion concentration - which will probably not be equal in all cases, those with the severest degree of cardiac failure and proportionate slowing of the circulation showing the peripheral signs most completely (97).

It is suggested that the slight increase above normal in the size of red corpuscles observed in the capillary blood of

many cases of congestive heart failure in this work, is probably related to the increased CO_2 and the tendency to acid reaction occurring therein, and that this enlargement results from physico-chemical changes, analogous to those occurring in vitro, in the presence of increased tension of CO_2.

Before applying this hypothesis more fully to the results in congestive heart failure, it might be helpful to discuss briefly the experimental and other evidence of various observers, on which the clinical evidence relating to congestive heart failure, as brought forward by this investigation, is considered to be based, and also to give a short description of the above-mentioned physico-chemical changes, and the mechanisms involved therein.

Increase in volume and diameter of red blood cells is experimentally known to occur with increased tension of CO_2 in the blood, or generally with increased hydrogen ion concentration. This phenomenon occurs parallel with that of the migration of chlorine ions from plasma to corpuscles (owing to the displacement of the Cl from dissociated NaCl ions in the plasma) which results in increase in corpuscular chloride and in plasma bicarbonate, more base being left in the plasma to combine with CO_2.

Hamburger (60) and von Limbeck (126) were among the early observers to recognise increase in size of the erythrocytes with increased CO_2, and the former also showed that the reverse action took place when CO_2 was removed from blood.

Price-Jones (113) deduced that variations in size of the corpuscles were due to alterations in blood reaction, as adding CO_2 and lactic acid to blood, increased the volume and diameter of the cells, while adding sodium carbonate decreased them. He further showed that red cell diameters became diminished on forced breathing, with decrease of the CO_2 in the blood, and is even of the opinion that CO_2 may possibly have a special swelling action on red cells out of proportion to its acidity (114).

Peters, Bulger and Eisenman (105) obtained an increase in cell volume with increase in CO_2 tension or hydrogen ion concentration, and in some experiments also, on adding lactic acid to blood.

Burger (17) states that red blood cells increase in an acid mixture, and decrease in an alkaline mixture, that this change in volume is a reversible one, and that under these conditions, the cells are not disturbed in their osmotic properties, behaving like untreated corpuscles when brought into hypertonic or hypotonic solutions.

Smirk (122) showed that CO_2 does not appreciably damage the cell membrane, as red cell volume was restored to normal on removing CO_2 from blood. He also found that oxygenation of venous blood caused a slight diminution in corpuscular volume, and in this connection, Wiechmann and Schürmeyer (129) have found red cell diameters to be slightly smaller in arterial than in venous blood.

The mechanism of the ionic interchange between corpuscles

and plasma in the presence of increased CO_2, with which increase in volume of the corpuscles is associated, is based on physico-chemical laws, which, as described by Lovatt Evans (42), depend on the presence in the corpuscles of weak acids - haemoglobin and phosphates - and on the permeability of the membrane to H_2CO_3 and to anions such as Cl.

Briefly described, when the tension of CO_2 rises in the plasma, both H_2CO_3 and Cl pass into the corpuscles through the membrane, and combine with available base mainly from haemoglobin, but to some extent also from phosphate, to form $KHCO_3$ and KCl, respectively, and the corpuscles become increased in size from the passage of water into them from the plasma, owing to the osmotic pressure of the corpuscular contents rising more rapidly than that of the plasma. Besides the passage of the anion Cl into the corpuscle, Lovatt Evans also states that the anion HCO_3 leaves the corpuscle in an attempt to establish equilibrium between the latter and the plasma.

As a result of this ionic interchange between corpuscles and plasma, the chloride and water contents of the corpuscles become increased, while the bicarbonate content of both the corpuscles and the plasma is also increased. Buffer substances present in the corpuscles are thus rendered available when the concentration of H_2CO_3 rises in the plasma, so that at higher CO_2 pressures, more CO_2 can be carried in the blood both by the red cells and the plasma (52).

When during a process of oxygenation of the blood, the

carbon dioxide is driven out, a passage of Cl ions and water takes place from the red cells into the plasma, and the former become diminished in volume. This has been shown experimentally by Henderson (67), and Joffe and Poulton (74), and probably explains the diminution in corpuscular volume occurring with oxygenation of venous blood (122), and the fact that according to Wiechmann and Schürmeyer (129), red cells of arterial blood are slightly smaller than those of venous blood.

The so-called "chloride shift" is very small when changes in CO_2 tension are within physiological limits (the oxyhaemoglobin - haemoglobin change being the more important mechanism in keeping blood reaction within normal limits), but it will assume greater proportions - from plasma to corpuscles - when the tension of CO_2 in the blood is raised above the normal limit. It also occurs to a greater or less extent, as stated by Harrison (62) in any acidosis or alkalosis, being most marked in acidaemia and alkalaemia, under which conditions, therefore, one might expect the red cells to be larger and smaller than normal respectively, in accordance with the fact that such changes in individual corpuscular volume are known to constitute a parallel phenomenon to the chloride shift.

Returning to the conditions present in congestive heart failure, the accumulation of carbon dioxide in the tissues from slowing and diminution of the blood flow, will from the foregoing experimental evidence, tend to cause a passage of Cl ions and water into the corpuscles of the peripheral capillary blood, and

an increase in their volume and diameter. This will be intensified by the factor of oxygen want, for as Lovatt Evans (43) has explained, a greater reduction of haemoglobin, with consequent liberation of more base, will tend to make the ionic interchange between corpuscles and plasma more extensive.

One may be permitted to reproduce here (translated from the German) Volhard's statement (quoted by Klein (76)), describing the exchange between the blood and the tissues under conditions of increased CO_2. He writes: "Under the influence of high CO_2 tension, there results an abnormal exchange between the tissue cells and the blood; the Cl ion and H_2O are taken from the blood to the tissues, and the cells of the latter become enlarged. This disturbance of the swollen cells takes place in those tissues where there is an exchange of molecules, and is a most important factor in the formation of oedema in heart cases."

It is not improbable, therefore, that a similar passage of Cl ions and water will tend to occur under those conditions from plasma to corpuscles in the peripheral blood in congestive heart failure, and lead to swelling of the corpuscles, especially as this is known to occur experimentally with increased CO_2 tension.

The increase in CO_2 tension of the peripheral blood, with the consequent tendency to increased acidity, upon which enlargement of the corpuscles in the manner described above, depends, will be governed by the extent to which reduction in circulation rate occurs, and the consequent extent to which tissue respiration is disturbed. In cases, for example, where there is less slowing

of the circulation, the accumulation of CO_2 in the tissues and peripheral blood will no doubt be proportionately less. Such cases would probably be those with only mild circulatory symptoms.

Another important factor must, however, be studied in the living body - namely, the ability of the lungs to eliminate CO_2 and adjust the blood reaction.

Increased pulmonary ventilation - due mainly to stimulation of the respiratory centre by oxygen lack - will wash out CO_2 from the blood, and help to adjust the blood reaction to a normal level. In this way, the rise in CO_2 pressure in the tissues may to some extent be prevented, although it should be mentioned that the simultaneous fall in oxygen pressure in the tissues with circulatory impairment may not be similarly prevented, as increased respirations do not materially increase oxygen saturation of arterial blood (59). Oxygen want in the tissues may thus be compensated for to a less extent than increase in CO_2. The latter may, in fact, be washed out to such an extent that, according to Fraser, Ross and Dreyer (49), an actual alkalaemia sometimes occurs in association with the dyspnoea of cardiac failure, although Harrison (63) has pointed out that such an alkalaemia can only occur so long as no gross pulmonary lesion is present.

It is more likely, on the other hand, that in severe congestive heart failure, as the experiments of Peters and Barr (104) have shown, the great increase of CO_2 in the capillary and venous blood from the effect of the subnormal circulation rate on

cellular respiratory function, together with the coincident impairment of pulmonary respiratory function, from congestion and oedema of the alveoli, usually present in such cases, may seriously interfere with a sufficient elimination of CO_2 from the lungs. The CO_2 tension in the alveolar air would therefore tend to be low in proportion to that in the arterial and venous blood.

Congestive heart failure may, under such conditions, therefore, be associated, as Wright (131) describes it, "with CO_2 accumulation and acidaemia".

Many observers have apparently related this fact to the dyspnoea of cardiac failure. Peters (103) concluded that the dyspnoea of cardiac decompensation was due to an absolute, or relative, CO_2 acidosis, resulting probably from impairment of the respiratory mechanism to discharge CO_2. A similar acidosis - sometimes uncompensated - from a relative surplus of CO_2 in the blood, is stated to occur by Loeb (79) in some cases of cardiac decompensation.

Pearce (102) in a case of cardiac failure, found evidence of a marked increase in CO_2 tension in the affluent blood of the lungs, and in the tissues, and states that the dyspnoea was due to a CO_2 storage, or acidosis, in the tissues.

De Wesselow (31) states that an acidosis may occur in decompensated heart disease from failure to excrete carbonic acid due to pathological changes in the walls of the alveoli, and such an acidosis is also stated to occur in the presence of pulmonary

lesions, by Fraser (48). The latter and his co-workers (50) have in fact recently shown that the carbon dioxide pressure may be raised in the arterial blood in the presence of the pulmonary lesions seen in severe congestive heart failure. Such a rise in arterial CO_2 pressure results from inefficient pulmonary ventilation, or inefficient gaseous exchange, and acts as an important additional stimulus to the respiratory centre.

In severe congestive heart failure, therefore, where an accumulation of CO_2 occurs in the tissues and in the capillary and venous blood from lowering of circulation rate, it is very probable, as many observers have stated, that, when a sufficient elimination of CO_2 is interfered with through impairment of the respiratory mechanism, there will be a tendency for acidaemia to develop from increased concentration of H_2CO_3.

Under such conditions, increase above normal in the size of red cells of the capillary blood in cases of congestive heart failure, where dyspnoea is usually a conspicuous feature of the clinical picture, may, in the light of known physico-chemical laws, represent evidence of the transport, by the cells, of more CO_2, and possibly of an attempt to increase the buffering capacity of the blood, through the mechanism of the chloride shift, to which enlargement of erythrocytes is, in the presence of increased CO_2, experimentally known to be a parallel phenomenon.

Besides, however, the tendency to disturbance of the acid-base balance of the blood in congestive heart failure, from an actual increased concentration of carbonic acid, reference must

be made to the possibility of a lactic acid acidosis, from the oxygen want in the tissues, and to that of an acidosis from secondary renal failure.

Meakins and Long (98) found an accumulation of lactic acid in the blood in severe circulatory failure with venous congestion, but state that this would not be sufficient, except in the most severe instances, to cause a conspicuous shift in either the carbon dioxide or oxyhaemoglobin dissociation curves. Further, in experimental circulatory stasis, Dautrebande, Davies and Meakins (30), and Peters, Bulger, Eisenman and Lee (107), found no evidence of the occurrence of a lactic acid acidosis. However, Clausen (23) did find an acidosis to occur in circulatory failure in children, especially in cardiac decompensation and anhydraemia.

Haldane (quoted by Mackenzie (91)) is inclined to relate the dyspnoea of cardiac failure to lactic acid. "The respiratory trouble in heart failure," he writes, "is due (at least mainly), to the slowed circulation, and consequent imperfect aeration of the tissues. The deficiency of O_2 in the tissues will cause increased formation of lactic acid, and consequent diminished alkalinity of the blood, and consequent necessity for an abnormally great removal of CO_2 from the blood."

Regarding acidosis from secondary renal failure, Wright (131) states that this may occur sometimes in the "cardio-renal" cases common in elderly subjects, and Meakins and Davies (96) found a moderate degree of such an acidosis to occur in a few cases, in the terminal stages of cardiac failure.

From the experimental evidence of increase in volume and diameter of erythrocytes occurring with addition of lactic acid to blood, or generally with a rise in its H ion concentration, it is probable that if accumulation of lactic acid occurs in congestive circulatory failure from gross oxygen want, or a retention of acids occurs from secondary renal failure, there will also be, with the tendency to diminished alkalinity of the blood, a similar increase in size of the red cells, if free elimination of CO_2 is prevented from the lungs, and the body is unable to utilize CO_2 excretion as a means of removing acid.

If there is any justification for the theory that has been advanced that increase in size of red blood corpuscles in congestive heart failure, represents evidence of an attempt, through the mechanism of the chloride shift, to increase the buffering capacity of the blood, under conditions where there is a tendency to a raised H ion concentration of the blood and tissues, one might expect evidence of some increase in the CO_2 combining power of the plasma.

That this, in fact, does occur, is shown by Peters, Bulger and Eisenman (106) who found a high plasma bicarbonate to be present in heart failure, in patients who regularly gave evidence of the presence of pathological changes in the lungs, which produced anoxic or "asphyctic" anoxaemia, and at the same time, interfered with the discharge of CO_2.

On the experimental side it may be mentioned that in experimental circulatory stasis, Dautrebande, Davies and

Meakins (30) found a chloride shift to occur into the red cells of venous blood, and an increase in the percentage of cells by the haematocrit method. Similarly, in experimental asphyxia, Kubo and Mitsui (77) found a chloride transference to occur from plasma to corpuscles. The volume of the latter was, however, not estimated.

Comment should now be made on the fact that although cases of mild heart failure were found to be associated with normal values for volume and diameter of the red blood corpuscles, a constant ratio between the severity of the cardiac failure and the degree of corpuscular enlargement was apparently not present in this investigation. Some cases had, in fact, normal values for the size of the red corpuscles in the peripheral blood, although according to their clinical states, they suffered from severe or fairly severe degrees of congestive heart failure.

It has been suggested that changes in the size of erythrocytes in cardiac failure are probably governed by the tendency to changes in blood reaction, and that in this respect, much depends on the ability of the lungs to excrete CO_2. A possible factor involved in explaining the lack of uniformity of the results in cases of severe heart failure may therefore be constituted by individual differences in the degree of impairment of pulmonary function for the discharge of CO_2.

The normal values for volume and diameter of red blood cells in cases of severe cardiac failure, where there is still the tendency to accumulation of CO_2 in the tissues and peripheral

blood from slowing of the circulation, may, possibly, be related to milder degrees of inefficiency of pulmonary ventilation, allowing a sufficient elimination of CO_2 to bring the pH of the blood to values within normal limits, under which conditions the chloride shift will probably be minimal, and therefore unaccompanied by recognisable enlargement of the corpuscles above their average normal size.

While at first sight, this suggested explanation may appear somewhat doubtful, in view of the fact that these cases in question apparently showed an approximately similar degree of dyspnoea, as far as could be gauged clinically, to that exhibited by cases where increase in size of erythrocytes above normal was recognised by the centrifuge and by cell measurement, it may be stated, as Fraser, Ross and Dreyer (49) have pointed out, that there is no method of gauging accurately the extent of hyperpnoea clinically, especially in patients seriously ill, and that such terms as orthopnoea and dyspnoea describe clinical appearances that cover a wide range of respiratory distress, and give probably no indication of true pulmonary ventilation.

As far as this investigation is concerned, however, it is considered that the severe dyspnoea exhibited by the majority of the cases with gross cardiac failure, has, in view of the associated corpuscular enlargement in these cases, probably indicated some degree of actual impairment of the respiratory mechanism for the discharge of CO_2, as previously discussed. The normal values for cell size were shown by only a few cases

of severe cardiac failure in this work, in which cases it is possible, that, according to the statement of Fraser, Ross and Dreyer (49), the dyspnoea has given no indication of true pulmonary ventilation, the latter being affected, it is considered, to a less degree than in the majority of the cases of cardiac failure above mentioned, where some enlargement of the erythrocytes above their average normal size was found to be present.

Broadly speaking, inefficiency of pulmonary ventilation would be likely to occur in cases with pulmonary disease, e.g., emphysema, in addition to heart failure, or in patients without additional pulmonary disease, but exhibiting gross lesions in the lungs occurring with severe congestive heart failure. It was precisely in such types of cases that Fraser and his co-workers (50) found the arterial carbon dioxide pressure to be raised, as a result of a degree of faulty ventilation sufficient to affect the efficient exchange of CO_2.

Applying the above general rule to the results obtained in the present investigation in relation to the type of lesion present, it was found that significant enlargement of the red blood cells was generally present in congestive heart failure occurring in patients with chronic bronchitis and emphysema, and in patients without such additional pulmonary disease but exhibiting well-marked signs of the pulmonary lesions associated with the cardiac failure itself. Regarding the latter type of case, however, certain facts emerging from the results require to be mentioned.

It was found, for example, that of the decompensated valvular lesions associated with significant enlargement of erythrocytes above normal, mitral stenosis predominated, while aortic regurgitation, with secondary mitral regurgitation and congestive failure, was more frequently associated with normal sizes of red cells, or only a probable enlargement of the cells above normal. When, however, in cases of aortic regurgitation, there was a co-existing pulmonary affection, such as emphysema, or the aortic lesion was combined with mitral stenosis, a significant enlargement of erythrocytes above normal was more likely to be present, although in one case with co-existing chronic bronchitis and emphysema, (Case 45) the results indicated only a probable corpuscular enlargement above normal.

Disturbance of pulmonary function will no doubt occur much earlier in congestive heart failure associated with mitral stenosis or pulmonary emphysema, than with pure aortic regurgitation, due to the fact that in mitral stenosis and emphysema, there is a tendency to lung involvement from increased pressure in the pulmonary circulation, even before cardiac failure develops - and which will be enhanced by the advent of the latter - while in aortic regurgitation, Lundsgaard and Von Slyke (84) state that the lungs are usually not often involved during the first stages of decompensation. Owing therefore to the added effect of earlier periods of pulmonary stasis in mitral stenosis and in emphysema, the degree of impairment of the respiratory mechanism for the discharge of CO_2, may often tend to be greater in such cases than

possibly even in the later stages of decompensation in aortic cases, when signs of pulmonary involvement are present. The fact that a significant enlargement of red cells above normal was more prone to develop in aortic cases when associated with chronic bronchitis and emphysema, or with mitral stenosis, would, in my opinion, be in keeping with the greater degree of impairment of pulmonary function occurring from the associated lesions.

A significant enlargement of red cells above normal was, however, present in one case of aortic regurgitation - No. 39 - with congestive heart failure associated with well-marked signs of pulmonary involvement, and with considerable dropsy. While this suggests the possibility of significantly enlarged erythrocytes above normal being present in pure aortic regurgitation in the stage of advanced decompensation with right-sided heart failure, I think, nevertheless, that the hydraemia or dilution of the blood associated, as later discussed, with the gross oedema, may have slightly influenced the size of the corpuscles, Burger (17) having stated that the ordinary osmotic properties of the erythrocytes are not interfered with when they enlarge in an "acid mixture". Further reference to the possibility of a specific influence of hydraemia on the erythrocyte will be made later.

Regarding the cases of severe congestive heart failure secondary to hypertensive conditions associated with myocardial degeneration, such as arterio-sclerosis and chronic nephritis, a significant enlargement of the erythrocytes above normal was present in all the cases of arterio-sclerosis and chronic

interstitial nephritis (including those not complicated by pulmonary emphysema) and a probable enlargement was present in the case of cardiac failure secondary to chronic parenchymatous nephritis.

As with aortic regurgitation, lung involvement in the above type of case, will tend to be of comparatively late occurrence, except when there is co-existing pulmonary emphysema, in which latter case, according to my view, a significant enlargement of the red blood corpuscles might be expected. The fact, however, that such enlargement occurred in those cases without additional pulmonary disease, indicates, in my opinion, the possibility of insufficiency of elimination of CO_2 through the lungs, in the presence of a pulmonary lesion secondary to severe congestive heart failure, resulting in the tendency to acidaemia, to which, as previously described, the enlargement of erythrocytes in the peripheral blood is considered to be related.

According to my view, apart from the primary factor of reduction in circulation rate, upon which depends the increase of CO_2 in the tissues and peripheral blood, an important additional or controlling factor in the enlargement of erythrocytes in congestive heart failure, is the extent of pathological changes in the lungs, upon which will depend the degree of impairment of the respiratory mechanism for the discharge of CO_2.

In other words, if in conjunction with the increased CO_2 content of capillary and venous blood, resulting from diminished circulation rate, a sufficient elimination of CO_2 through the

lungs is, as stated by many observers (31), (79), (102), (103), (104), (131), seriously interfered with, owing to the altered condition of the pulmonary epithelium, a significant enlargement of the red corpuscles will, in my opinion, tend to occur in association with the resulting CO_2 accumulation and tendency to acidaemia. On the other hand, if the degree of impairment of pulmonary ventilation affecting carbon dioxide is less marked (in which connection the type of lesion may be of some significance, as previously discussed) the increased CO_2 in the tissues and peripheral blood will tend to be more completely washed out, and there will consequently be less tendency to acidaemia. This may, I think, afford a possible explanation for the fact that in severe cardiac failure, the red cells are occasionally only probably enlarged above normal, and may even show no deviation in volume or diameter from the normal. It should be stated, however, that while such exceptions may occur, it is apparently more common, according to my investigations, for severe congestive heart failure to be associated with significantly enlarged red cells above normal.

The apparent failure of enlarged red cells to exhibit further enlargement with increase in severity of the cardiac failure, observed in a few cases with proximity of death, is difficult to explain. It may possibly be due to some changes occurring at this stage, in the corpuscular membrane, as regards permeability to salts and water, and interfering with the extent of the ionic interchange between corpuscles and plasma.

With regard to the significantly smaller than normal red

cells in the three cases of cardiac failure where infective endocarditis was present, as an infection on old valve lesions, it is considered that the loss in volume and diameter is due to direct degenerative changes related to the destructive toxins in the blood (22). In other words, these cases have exhibited the predominating effect of degenerative or "katabiotic" factors relating to the infection, on the size of the red corpuscles, rather than the effect of the physico-chemical factors previously described.

It was observed that in no other type of case in this work was the stage of heart failure associated with a significant diminution in size of the red cells below normal, which suggests that a decrease from physico-chemical factors, such as may result from an alkalaemia due to an excessive washing out of CO_2, is not usually present in the peripheral blood in congestive heart failure.

Comment must be made on the enlargement of red blood cells in cases of congestive heart failure exhibiting gross oedema, amounting to general anasarca, with which, as noted in the analysis of the results, a relatively diminished red cell count and haemoglobin percentage, was associated. As will be further discussed in a subsequent section, a condition of hydraemia or dilution of the blood has presumably been present in association with the relatively lowered erythrocyte count and haemoglobin percentage in the oedematous stage of these patients, which gave way to a concentration of corpuscular elements when

subsidence of oedema occurred, following a profuse diuresis.

Herz (quoted by Capps (22)) has stated that dropsy from any cause brings about an "acute swelling" of the red corpuscles, but Capps himself failed to observe such a specific influence of hydraemia on the erythrocyte in the cases of nephritic dropsy which he studied.

In this investigation, the significant enlargement of red cells above normal in cases where gross cardiac oedema with an apparent dilution of the blood was present, suggested the possibility of a specific influence of the hydraemia on the erythrocyte. It was, however, noted that only a slight diminution in volume and diameter of the cells occurred with subsidence of oedema following diuresis, so that any specific influence of the diluted blood on the red cell has, according to my observations, only been slight, as demonstrated by the centrifuge or by cell measurement.

Although the erythrocytes showed the above-mentioned tendency to diminution in volume and diameter with subsidence of oedema following diuresis, a return to normal values was apparently only obtained after further clinical improvement had occurred, and the signs of cardiac failure had practically disappeared.

Henderson (67) has shown that increase in oxygen pressure causes a movement of chloride outwards from the cells, and a diminution in their volume - i.e., the reverse of what occurs with increase in CO_2 pressure. Joffe and Poulton (74) also found that oxygenation of the haemoglobin drove out CO_2 from the corpuscles, which was associated with a diffusion of acid radicles out of them, and a diminution in their volume.

Administration of oxygen raises the alveolar oxygen tension,

so that the gas is diffused more readily into the blood, and the tendency to slight reduction in volume and diameter of red cells in this work which rapidly occurred with inhalation of oxygen, suggests that from the foregoing experimental evidence, some CO_2 has been driven out of the cells, and has been associated with a passage of chloride and water outwards into the plasma.

While only a very slight diminution in size of the erythrocytes was observed after oxygen inhalation, a more marked decrease with usually a return to normal values was associated with further clinical improvement, and the re-establishment of a state of "compensation", with removal of the signs and symptoms of cardiac failure. Under such conditions, with increase in the minute volume of the circulation, and improvement in, or disappearance of, the pulmonary complications, there will be a removal of the factors which, as previously described, have been held largely responsible for the increase in size of the corpuscles above their average normal size.

A diminution in size of the erythrocytes with circulatory improvement, but not entirely with a return to normal values, was observed in a patient in this work where the cardiac failure was secondary to emphysema and chronic bronchitis, in whom, after the heart failure had subsided, the red cells were apparently still slightly larger than those of healthy persons, the mean diameters, according to the standard of differences, showing a probable increase above normal. This result appeared to be in agreement, to some extent, with the observation of Price-Jones (114) that red blood cells are enlarged in emphysema, although it was noted that a similar type of result was not obtained when improvement from congestive heart failure occurred in three other patients,

in whom emphysema and chronic bronchitis were also present, although not actually the primary cause of the cardiac failure. Even in the case above referred to, however, it was seen that the enlargement of the corpuscles was enhanced by the cardiac failure, presumably, it is thought, because of the increase in carbon dioxide in the tissues and peripheral blood from slowing of the circulation, together with increase in the degree of impairment of respiratory exchange from the additional factor of congestion and oedema of the lungs, so that there has been a greater tendency to "CO_2 accumulation and acidaemia" (131).

Before concluding this section of the discussion, it should be mentioned that the question may be raised as to whether the slight increase in size of the erythrocytes above normal frequently observed in the peripheral blood in congestive heart failure, is, instead of being related to CO_2 and blood reaction, in the nature of a compensation for anoxaemia, and analogous to the enlargement occurring in Vaquez's cases of cardiac disease with chronic cyanosis (124). This point will, however, be more conveniently discussed in a subsequent section of the discussion, in conjunction with the associated changes in the number of erythrocytes and in their individual haemoglobin content.

II. Number of Red Cells, Haemoglobin Percentage and Haemoglobin Content of Red Cells.

The results in this investigation confirm what has been stated in the literature - namely, that a rise in the number of red cells in the peripheral blood frequently accompanies a condition of cardiac failure, associated with dyspnoea, cyanosis and venous congestion. In addition to this, it has also been shown that with improvement from congestive heart failure, a decrease occurs in the red cell count, which in the majority of the cases returned to a normal, or slightly diminished figure, although in a few cases, it remained slightly raised above normal.

The haemoglobin percentages have, generally speaking, not paralleled the extent of the increase in the red cell counts, being, in fact, in some cases, relatively low in the stage of cardiac failure, as compared with the high erythrocyte counts. Some disparity was thus present between haemoglobin and red cells in congestive heart failure, so that the latter has tended to be associated with subnormal values for colour index.

Compared with the range of values for red cell count in congestive heart failure stated to occur by one of the writers quoted in the literature, namely, Anders and Boston (4) 5,000,000 to 8,000,000 per cmm., and by Panton and Marrack (101) 7,000,000 to 8,000,000, the range in the present investigation for the counts over 5,000,000, has been generally lower - namely, 5,200,000 to 7,000,000. Nevertheless, a few cases had red cell counts of 6,000,000 per c.mm. and over this figure up to 7,000,000,

together with haemoglobin percentages above normal.

Regarding increase in the number of red blood cells in congestive heart failure, two possibilities must be considered, namely, the occurrence of a relative increase in red cells (described as a relative, local polycythaemia) and the development of a secondary, absolute increase in red cells, described as an erythrocytosis.

A relative polycythaemia may be shown to be present (Fitz (47)) by an increase in red cell count combined with evidence of diminished plasma volume, obtained most simply by the haematocrit. While this type of increase in the number of red cells is of frequent occurrence in conditions associated with loss of water from the body (as for example in choleraic diarrhoea), it can also occur, as stated by Grawitz (quoted by von Limbeck (127)) from loss of water from the blood alone.

Dautrebande, Davies and Meakins (30) found a passage of fluid to occur from the blood to the tissues in experimental circulatory stasis, to which they attributed the relative increase in red cell count and haemoglobin percentage and the increase in total red cell volume (as indicated by the haematocrit) which occurred under these conditions.

In this investigation the increases in total red cell volume (as shown by haematocrit readings), red cell count, and haemoglobin percentage, would probably also indicate that concentration of the corpuscular elements of the peripheral blood had occurred in many cases. Disappearance of such a relative

polycythaemia would no doubt depend on increase in circulation rate, which has probably operated in those patients who, with improvement in clinical condition, exhibited in the peripheral blood a decrease in red cell count, a return to normal haematocrit readings, and, as an indication of increased velocity of blood flow, a reduction in blood viscosity.

Loeb (80), in his monograph on oedema, states that in cardiac decompensation, conditions are present in association with the venous obstruction and increased permeability of the capillaries, for an increased transudation of fluid from the blood to the tissues, which is an important mechanism in the subsequent oedema.

It has been noted in this investigation, by correlating the results to the clinical condition, that demonstrable oedema (usually "moderate", but in two cases "marked") was present in the majority of cases of congestive heart failure, exhibiting red cell counts above normal in the peripheral capillary blood which sometimes amounted to 6,000,000 per c.mm. and over. De Wesselow (32) considers that the demonstration of a high red blood cell count or increase in red cell volume in cases of oedema, suggests a tissue, or pre-renal origin of dropsy, that is, an abstraction of water from the blood by the tissues. While it is not the purpose of this thesis to discuss the mechanism of cardiac oedema, which must include other factors besides increased capillary permeability such as osmotic pressure of plasma proteins and secondary interference with renal function, nevertheless, it is possible that the presence of oedema in cases of congestive

cardiac failure in association with increase in red cell count and total corpuscular volume, may indicate, according to De Wesselow, that concentration of the red cells has taken place from abstraction of water to the tissues. In other words, this may support the conclusion that a relative increase in the number of red corpuscles occurs in the peripheral blood in severe congestive heart failure.

In addition, however, to the increase in red cells in the peripheral blood in congestive heart failure being merely in the nature of a so-called relative polycythaemia, there is the possibility, previously mentioned, that it may also be related to an actual erythrocytosis or secondary absolute increase in red cells. Such an erythrocytosis would act as a compensation for oxygen want, the latter resulting from the stagnant anoxaemia depending on reduction in circulation rate, and enhanced by the factor of anoxic anoxaemia resulting from associated gross pulmonary lesions. As indicated in the résumé of the literature, an erythrocytosis is stated to occur by many writers in association with the cyanosis of failing circulation and imperfect oxygenation of the tissues.

Slowing of the circulation produces stagnant anoxaemia from an excessive proportion of oxygen used up in the systemic capillaries and this will favour cyanosis. The latter will, however, tend to be enhanced by arterial or anoxic anoxaemia, from incomplete re-oxygenation of blood in the lungs, in the presence of gross pulmonary lesions secondary to severe congestive heart failure, together with, in those cases where it is present, pulmonary

disease such as emphysema and chronic bronchitis, in addition to heart failure.

It was noted in this work that higher figures for red cell counts were generally present in patients with severe cardiac failure, exhibiting a marked degree of cyanosis, but definite evidence that such high erythrocyte counts in the capillary blood relate to an actual erythrocytosis can only be obtained by an estimation of total blood volume. This would then tend to be in excess of normal, as compared with the decreased, or possibly normal, blood volume of relative polycythaemia (Rowntree and Brown (118)), despite the fact that in the latter condition, these observers state (118) that the number of erythrocytes or the percentage of cells, as determined by the haematocrit method, may be high.

However, that an increment of red cells has possibly occurred in association with the greater degree of oxygen want of the tissues resulting from pulmonary complications with their tendency to anoxic anoxaemia, may possibly be seen from the fact that the inhalation of oxygen (which relieves arterial anoxaemia) has in the four patients in whom its effects were studied, caused a slight but consistent diminution in the red cell count, together with a reduction in cyanosis.

It is worthy of comment that, while all the above cases had well-marked pulmonary lesions secondary to heart failure, three of them had emphysema and chronic bronchitis, in addition to the heart failure. Such a chronic pulmonary affection will, apart from cardiac failure, give rise to a tendency to cyanosis from

deficient oxygenation of blood in the lungs, and as French (51) has stated, to some degree of compensatory increase in the number of red blood cells. Sometimes also in mitral stenosis - which was the lesion in the fourth case in which the effect of oxygen was studied - a compensatory increase in the number of red cells may, according to French (51), occur, in order to distribute the haemoglobin over a larger corpuscular area. It was noted that in the patient with mitral stenosis referred to above, a red cell count of 5,420,000 per c.mm. was present after considerable improvement in condition had occurred, and that in one of the patients with chronic bronchitis and emphysema, a count of 5,570,000 per c.mm. remained after improvement from the cardiac failure had taken place. While these counts represent only moderate increases above the normal standard, they may nevertheless indicate the tendency to increase in the number of red cells in such cases apart from gross cardiac failure (51).

Regarding the possible mechanisms involved in an erythrocytosis consequent upon oxygen want, Parkes Weber (128) states that he found evidence of abnormal haematopoietic activity of the bone-marrow at autopsies on cardiac cases with chronic cyanosis, but Vaquez (125) has remarked on the fact that no nucleated red cells or myelocytes are found in the blood of such cardiac cases with cyanosis, where an increase in the number of red cells is present.

It is also interesting to note, - from the very few references that I could find in the literature, - that the reticulocytes are apparently not increased in cardiac cases exhibiting erythrocytosis. Harrop (65), for example, quotes a

case of cardiac disease with erythrocytosis, in which the red cell count was 6,100,000 per c.mm., and the percentage of reticulocytes was 0.6, which is within normal limits. In another two cardiac cases (the erythrocyte counts of which are, however, not given) the reticulocytes were 0.9 per cent. and 0.5 per cent. of the red cells, being also apparently within normal limits.

Nevertheless, Parkes Weber's observations on the activity of the bone marrow (which is, after all, an important source of red corpuscles in response to oxygen want) cannot be disregarded, in spite of the foregoing apparent lack of evidence in the blood stream, because, as McDowall (88) points out, there may be an increase in red cells in circulatory disease, without the presence of abnormal or primitive forms.

In the chronic form of cardiac failure under discussion, with failure of the general circulation and venous congestion, it is possible that the high red cell counts in the peripheral blood -especially those from 6,000,000 to 7,000,000 cells per c.mm. - may be related to an erythrocytosis as well as more directly to a relative polycythaemia, the erythrocytosis resulting from some degree of over-activity of the bone marrow, in response to anoxaemia and cyanosis arising from slowing of the circulation and peripheral stasis, together with deficient reoxygenation of blood in the lungs from congestion and oedema of the alveoli. The latter factor will be intensified in cases with pulmonary disease (e.g., chronic bronchitis and emphysema) in addition to heart failure.

It appeared from the results of this investigation that the polycythaemia of congestive heart failure may be most marked in cases of mitral stenosis when compensation has failed, and in patients with cardiac failure in whom chronic bronchitis and emphysema are present, either constituting the primary cause of the failure, or present as co-existing lesions with other conditions - such as, for example, chronic interstitial nephritis - with which the cardiac failure is associated.

Another mechanism for supplying additional red cells to the circulation, besides that relating to the bone marrow, must now be mentioned, namely, that of splenic contraction.

The spleen is a reservoir of red cells which it can discharge into the circulation under certain conditions (8), and Barcroft and Poole (9) have shown that it can concentrate blood - in other words, that blood taken from splenic pulp is more concentrated in red cells and haemoglobin than blood taken from the peripheral circulation at the same time.

Wright (132) states that splenic contraction can be shown to occur in response to oxygen want from any cause, and it is interesting to note the statement of McDowall (89) that contraction of the organ may be experimentally shown to occur under conditions also of carbon dioxide retention.

Williamson (130) considered the erythrocytosis of experimental oxygen want, to be due to splenic contraction; and Harrop (64) was of the opinion that in the erythrocytosis occurring at high altitudes, the first stage, which appeared rapidly and was

not attended by evidence of formation of new blood, was also due to expression of red cells from the spleen. In asphyxia, Scheunert and Binet, and their respective co-workers (quoted by Barcroft and Poole (9)), obtained an increase in red cells in the circulating blood, and noted that in the majority of the cases, the polycythaemia occurred in normal animals, but not in splenectomised animals.

It is suggested, from the foregoing evidence of splenic function in relation to oxygen want, that if an increase in red cell count observed in the capillary blood in congestive heart failure is related to an actual erythrocytosis, the spleen may play a part in furnishing some of the additional erythrocytes, possibly for more immediate requirements, or in the earlier stages, before the bone marrow has properly assumed its rôle.

It may be of interest to mention the recent experiments of Brednow, quoted by Goldblatt (54) on the influence of CO_2 on blood volume. Estimations of plasma and erythrocyte volume were carried out before and after breathing mixtures, containing high CO_2 percentages, and it was found that a shift in blood reaction to the acid side led to an increase in circulating plasma and red cells, and that under these conditions, the venous blood pressure rose.

As in cardiac failure with venous congestion, the tension of CO_2 tends to be increased in the tissues, and the venous pressure to be raised, the increase in red cells may also be related, as the above experiments appear to suggest, to increased carbon

dioxide, with which splenic contraction, according to the statement of McDowall (89) would also appear to be in keeping. However, the total blood volume, as previously mentioned, would require to be estimated to show that the increase in number of red cells was really in the nature of an absolute polycythaemia.

To sum up, as total blood volume was not estimated, the results of this investigation can only confirm, from the evidence of raised red cell counts, and diminished plasma volume - the latter obtained from the haematocrit - that as stated in the literature, a relative increase in the number of red cells has occurred in the peripheral capillary blood in congestive heart failure. The extent of such a relative polycythaemia will no doubt depend on the degree of reduction in circulation rate, which will vary with the severity of the circulatory failure. It was, in fact, found that in cases with less severe degrees of heart failure - where there is presumably less proportionate slowing of the circulation - normal red cell counts, or counts only slightly above normal, were obtained.

While this investigation confirms the occurrence of a relative or apparent polycythaemia in the peripheral blood, it is nevertheless suggested that an erythrocytosis may also have occurred in congestive heart failure - especially in those cases with red cell counts over 6,000,000 per c.mm. - in relation to oxygen want and cyanosis, which would be in keeping with statements in the literature that such an erythrocytosis frequently occurs in association with the cyanosis of failing circulation.

Under such conditions, it is suggested that the spleen, as well as the bone marrow, has probably played a part in supplying additional red cells to the circulation.

Regarding the point that the haemoglobin percentages have, generally speaking, not been increased to the same extent as the red cell counts in congestive heart failure, this is to some extent in keeping with the fact that in polycythaemia, it is usual for the haemoglobin to be increased to a less degree than the number of red cells, which French (51) states applies to all causes of polycythaemia.

While this may apply to those cases where increased haemoglobin percentages above normal were found to accompany red cell counts in the neighbourhood of 6,000,000 per c.mm. and over, it may not explain the disparity between haemoglobin and red cells observed in cases where the counts were increased above normal, although not amounting to 6,000,000 per c.mm., but where the haemoglobin percentages were not correspondingly increased above the average normal value.

A suggested explanation for this feature of relatively high red cell counts compared to the haemoglobin percentages, is given by Ashe (7) previously mentioned in the literature, who included kidney function in his study of blood counts in congestive heart failure, and related the disparity between haemoglobin and red cells to the fact that the former was apparently more proportional to the associated impairment of renal function - and the tendency to anaemia therefrom - than the red cells which by reason of

peripheral stasis, were in many cases relatively high. He showed that such renal function impairment may occur in pure cardiac cases with decompensation - in other words, apart from actual renal lesions. The renal dysfunction in the cardiac cases would no doubt be due to circulatory insufficiency and passive congestion. Ashe concluded that the type of blood count which usually characterised congestive myocardial failure, was one in which the number of red cells was relatively high compared to the haemoglobin percentage, so that the colour index tended to give a low value.

The results of this investigation are, to some extent, in agreement with those obtained by Ashe, in so far as many of the cases exhibited increased red cell counts above normal in association with haemoglobin percentages that were not increased above the average value for the normal individuals. In some of these cases, in fact, the haemoglobin percentage was below this value. Nevertheless, a small number of cases was found to exhibit increased haemoglobin values above normal, together with raised erythrocyte counts, although the latter were proportionately more increased than the former. These cases comprised patients with mitral stenosis, and/with chronic bronchitis and emphysema, and were the cases previously mentioned as having counts which ranged from 6,000,000 to 7,000,000 red cells per c.mm.

It should be noted, however, that a polycythaemic blood count of haemoglobin as well as of red cells, was not an invariable rule in cases of congestive heart failure secondary to mitral stenosis

or associated with chronic bronchitis and emphysema, although an increase of red cells was usually present.

Ashe (7) found relatively high red cell counts to be present even in cases of cardiac failure occurring in the course of chronic nephritis, where moderate, or in some cases, marked impairment of renal function was demonstrated, although similar degrees of diminution in kidney function from uncomplicated Bright's disease, or such conditions as polycystic kidney and nephrectomy were invariably associated with a fairly well-marked secondary anaemia, characterised by diminution in the number of red cells as well in the haemoglobin percentage.

In the two cases of chronic interstitial nephritis and secondary congestive heart failure studied in this work, high red cell counts were also obtained, the count in one case - where, however, chronic bronchitis and emphysema were also present - amounting to over 6,000,000 red cells per c.mm.

In a few cases, however, with a marked degree of renal inadequacy, Ashe did obtain low values for red cell count and haemoglobin percentage, due, in his opinion, to the fact that, in spite of the congestion associated with the cardiac failure, the anaemia of the marked renal lesion played the principal part in the blood picture.

It is considered that increase in impairment of renal function may similarly help to explain the apparently exceptional diminution in erythrocyte count and haemoglobin percentage observed with increase in the heart failure in Case 37 of this investigation, the patient with chronic parenchymatous nephritis and secondary cardiac failure. The suggestion that the blood changes in this

case, at the time of the second examination, represented an anaemia dependent on a greater degree of diminution in kidney function, is supported by the fact that the blood-urea content at this stage was found to be 124 mg. per cent., while at the time of the first observation, it was 72 mg. per cent. It should be stated, in connection with this particular patient, that although she had renal symptoms and urea retention, she was clinically a case of heart failure.

With increase in severity of the cardiac failure, it was apparently more usual, as shown by the results in this investigation, for the blood to exhibit an increase in red cell count, and, to a less degree, in haemoglobin percentage - that is, to retain the characteristic features of the blood count in congestive heart failure - in spite of the fact that with increased congestion more impairment of renal function might logically be expected. Nevertheless, the case of chronic parenchymatous nephritis and secondary cardiac failure referred to above, showed that it is apparently possible for the blood, at a stage when there is more marked renal inadequacy, to exhibit the features more in keeping with the latter than with cardiac failure, and to be characterised by a diminution in both the number of red cells and the haemoglobin percentage.

Apart from this case of parenchymatous nephritis and secondary heart failure, a small number of cases was found to exhibit blood changes of the "secondary anaemia" type - that is, characterised by a relatively greater diminution in haemoglobin percentage than

in red cell count - in the stage of heart failure with congestion. Excluding the cases exhibiting gross oedema, which require special mention, these blood changes were present in the three patients with infective endocarditis and cardiac failure, and in four patients with aortic regurgitation and failure of compensation.

The anaemia was most severe in the cases of infective endocarditis, where there was particularly a marked diminution in haemoglobin percentage, and low colour indices. Further, one of the cases showed that the anaemia tended to be progressive in character. In describing infective endocarditis, French (53) writes: "The occurrence of a progressive anaemia in chronic heart cases always arouses suspicion of fungating or infective endocarditis; most cases of fungating endocarditis present symptoms of failing compensation which are often very difficult to distinguish from those due to the mechanical effects of chronic valvular disease, so that it is often difficult to distinguish a heart case without fungating endocarditis from one in which fungating endocarditis has supervened."

In such cases, therefore, the evidence supplied by the blood count such as above described, would arouse suspicion of infective endocarditis, especially if this evidence was supplemented by such clinical phenomena as petechial haemorrhages in the skin, enlargement of the spleen, haematuria, and pyrexia not explained by intercurrent infection. The presence of micro-organisms in the blood, as a result of cultural examination, would, of course, settle the diagnosis.

It was noted that, in spite of well-marked signs of pulmonary

congestion, cyanosis was not present in two of the cases of infective endocarditis and cardiac failure studied in this work, and was only very slight in the remaining case.

Anaemic patients are known to exhibit less tendency to cyanosis than individuals with a normal amount of haemoglobin, and in one of the above-mentioned three cases the haemoglobin percentage (31 per cent.) has probably been too low, according to the observations of Lundsgaard (83) to raise the amount of reduced haemoglobin above the threshold for cyanosis.

The blood changes in the four cases of aortic regurgitation, previously referred to, were those of a moderate secondary anaemia, with a slight reduction in the number of erythrocytes and a relatively greater diminution in haemoglobin percentage. Gulland and Goodall (58) have stated that the red cell count is not usually raised in aortic regurgitation with failure of compensation, with which the results in these four cases are apparently in agreement.

Another case of aortic regurgitation with failure of compensation in this work (No. 39), also had a diminished erythrocyte count and haemoglobin percentage, but this case is not included in the above-mentioned group, because gross oedema was present, to which the diminution in haemoglobin and red cells appeared to be related. This is a point to which subsequent reference is made. However, even after marked diuresis, with an associated increase in the number of cells and in the haemoglobin percentage, the peripheral capillary blood still exhibited a moderate secondary anaemia.

It would appear, however, that Gulland and Goodall's statement regarding the blood count in aortic regurgitation with failure of compensation, does not apply to all cases, for one such case in this work (Case 49) was found to exhibit, in the stage of cardiac failure with congestion, a slight rise in red cell count above the average normal value of approximately 5,000,000 per c.mm. In addition, even in the previously mentioned group of four cases, one case (No. 36) showed a slight rise in erythrocyte count with increase in severity of cardiac insufficiency. The increase in the number of red cells in the peripheral blood in this case is probably due to a greater degree of passive congestion of the subcutaneous circulation occurring in the more advanced stage of decompensation.

Associated with the usual absence of polycythaemia in aortic cases is no doubt the fact that cyanosis is, as a rule, not a prominent clinical feature. Lundsgaard and Van Slyke (84), commenting on cyanosis in aortic regurgitation, state that this occurs only in the more advanced stages of decompensation, when cardiac insufficiency is very pronounced, as the lungs are not usually involved in the first stages, and it is very difficult for a decreased minute volume output of the heart alone to cause cyanosis, through increased oxygen consumption in the tissues, unless reinforced by much stasis.

While the red cell counts are not usually raised in pure aortic insufficiency with failure of compensation this investigation has shown that when the aortic valvular lesion was

associated with a co-existing chronic pulmonary affection, such as chronic bronchitis and emphysema, or when it was combined with mitral stenosis, raised erythrocyte counts were generally the rule. These cases have also exhibited more marked cyanosis, no doubt due in part to the earlier involvement of the lungs, through increased pressure in the pulmonary circulation from the nature of the associated lesions.

With regard to the cases with generalized oedema (including the previously mentioned case of aortic regurgitation - No. 39), where diminished red cell counts and haemoglobin percentages were present in the markedly oedematous stage and an increase in count and in haemoglobin percentages characterised subsidence of oedema following a good diuresis, Strauss and Beckmann (both quoted by Loeb (81)), state that hydraemia, or dilution of the blood, may occur in certain stages of cardiac oedema. In determining the presence of hydraemia Loeb (82) attaches great value to variations in the erythrocyte count, which he considers to be more reliable than variations in the plasma proteins.

The figures for red cell count and haemoglobin percentage in the oedematous stage of the above-mentioned cases, would therefore represent relative diminutions, and be associated with a condition of hydraemia. The diminished blood viscosity found in these cases would also be in keeping with a diluted blood (58) (69). That these are relative reductions may be seen by the apparently rapid increase in count, haemoglobin and viscosity, following dehydration with diuretics.

The association of moderate, and in two cases, of marked oedema with increased red cell counts above normal, has already

been mentioned. These cases also had raised values for blood viscosity.

It should be stated that a hydraemic change in the composition of the blood does not necessarily mean hydraemic plethora, with increase in blood volume. De Wesselow (33) states that the blood volume in hydraemia is unaltered or diminished, and that the presence of a true hydraemic plethora in cardiac hydraemia is uncertain. Rowntree and Brown (119), however, demonstrated increased blood volume during the stage of oedema in some cases of cardiac disease, and Bolton (14), in experimental passive congestion, also noted the occurrence, at one stage, of a hydraemic plethora in the vessels.

However, while from a study of the variations in red blood cell counts and haemoglobin percentages in some cases in this investigation, exhibiting marked general dropsy, a condition of hydraemia may be presumed to have been present in the oedematous stage, no conclusions can be drawn as to the presence of a hydraemic plethora.

With regard to the haemoglobin content of the individual red cells in the peripheral circulation in congestive heart failure, the results in this investigation indicate that, on the average, this is somewhat lower than normal. This, to some extent, confirms the observation of Ashe (7) that congestive heart failure is characterised by a low colour index.

While due in a few cases to blood changes of a "secondary anaemia" type, this tendency to a low colour index is mostly due

to the fact that as previously commented on, the haemoglobin percentages in congestive heart failure are proportionately less increased than the red cell counts, their values in some cases being relatively low compared to the high red cell counts. With improvement from congestive heart failure, the colour index tended to show a slight increase in value, which depended on the fact that the decrease in red cell count under those conditions, occurred to a greater extent than that in haemoglobin percentage.

Some comment may now be made on the question mentioned in the previous section, as to whether the increase in size of red cells frequently observed in the peripheral capillary blood in severe congestive heart failure, is analogous to the corpuscular enlargement found by Vaquez (124) to occur in cardiac cases with chronic cyanosis, consisting chiefly of congenital heart disease, where the enlargement was regarded as a defensive reaction against anoxaemia. It is appropriate to make this comment at this stage, as it involves another previously mentioned point, namely, the relationship of the size of the erythrocytes to their content of haemoglobin, the significance of which has not yet been referred to.

Vaquez's principal findings may be described again, in order to see how they compare with those obtained in this investigation. Vaquez (124) found that in his cases, the progressive increase in size of the erythrocytes was a phenomenon which did not occur at the same time as the increase in number of the corpuscles,

polycythaemia being usually well established before the corpuscles began to grow in size. When the corpuscular enlargement was eventually present, the average diameters usually measured 8 μ or over, and in one case, actually approximated a measurement of 12 μ.

Regarding the relationship between the size of the erythrocytes and their content of haemoglobin, Vaquez made the important observation that an increase in the latter accompanied the increase in size of the cells, so that the over-sized erythrocyte carried a high complement of haemoglobin. "Le globule rouge," he writes, "est, à la longue, chargé d'une quantité plus considerable d'hémoglobine, en même temps que son volume s'accroît."

It would appear that in these cases of congenital heart disease with long-standing cyanosis, the slowly progressive enlargement of the red corpuscles, accompanied by corresponding increase in their individual haemoglobin content, is, following the increase in their numbers, a further attempt on the part of nature to combat the anoxaemic process, and increase the respiratory capacity of the blood.

As to the nature of this type of corpuscular enlargement, associated with increase in haemoglobin content, Capps (22) has observed that macrocytes rich in haemoglobin can only result from biotic factors - that is, factors concerned with the growth and development of the cells. Vaquez (125) in "Diseases of the Heart" states that the blood in the type of cardiac case above-mentioned (124), - namely, that associated with chronic cyanosis - contains no nucleated red cells or myelocytes, and

therefore suggests that the abnormality in size of the red cells found in such cases should be called a "cellular hypertrophy", which, in other words, indicates an increased development of the normal erythrocyte.

The facts emerging from the results obtained in this work in congestive heart failure show important differences from those emerging from Vaquez's results.

A more rapid increase in the size of individual red cells has apparently occurred in congestive heart failure - as seen from a study of cases exhibiting exacerbations of the cardiac failure - and this increase in size was found to accompany more or less the increase in the number of the cells. Again, the red cells in congestive heart failure were, on the whole, found to be increased in size to a less degree than those in Vaquez's cases.

An extremely important difference is also seen in the relationship between the size of the red cells and their haemoglobin content, in so far as the latter in congestive heart failure was relatively low in relation to the over-sized erythrocytes. The curves for volume index and mean diameter of the red cells, and those for colour index in Figures 1, 2, 3 and 4, have tended at times to be inverse in direction, and have shown that, contrary to what Vaquez (124) observed in his cases, no parallel increase in corpuscular content of haemoglobin has apparently occurred in association with the increase in size of the corpuscles.

From the foregoing comparison with Vaquez's observations in

congenital heart disease with chronic cyanosis, the tendency to enlargement of red blood cells in congestive heart failure is, in my opinion, not due to the same physiological mechanism as that operating in Vaquez's cases, in other words, it is not in the nature of a cellular hypertrophy, occurring in response to the stimulus of oxygen want, although indeed it has frequently been found to be present together with a marked degree of cyanosis and a noticeable increase in the number of erythrocytes.

It is suggested that although the two conditions of oxygen want and increase in carbon dioxide exist together in the peripheral circulation in congestive heart failure, as a result of lowering of the circulation rate with its effect on tissue respiration, the method by which the organism attempts to combat these disturbances is different in each case. In other words, while the increase in the number of erythrocytes above referred to is probably an attempt to compensate for the anoxaemia, it is considered that the increase in size of red blood cells in the peripheral blood in congestive heart failure is related to the increased carbon dioxide, being a phenomenon based, as previously discussed, on the physico-chemical laws governing the ionic interchange occurring between corpuscles and plasma in the presence of increased concentration of H_2CO_3.

It has been further suggested that the increase in size of red cells found to be present in many cases of gross congestive failure represents evidence of the transport by them of more CO_2 and of an attempt, through the parallel phenomenon of the chloride shift, to increase the buffering capacity of the blood under conditions where

there is a tendency to acidaemia from inefficiency of pulmonary ventilation for the elimination of CO_2.

III. Viscosity of the Blood.

The evidence brought forward by the results in this work appears fairly conclusive that the viscosity of the blood in congestive heart failure stands in relation to the number and size of the red cells. It has not only been shown that increase in viscosity in the stage of failure is associated with increase in number or size of the erythrocytes (being most marked when increase in both is present) but it has also been demonstrated that the reduction in viscosity with improvement from cardiac failure, and noted as occurring also after oxygen administration, and venesection, is associated with coincident diminution in number and size of the cells.

It appeared, however, that the red blood cells, although known to play an important part in blood viscosity (121), might not be the only factors responsible for the hyperviscosity of congestive heart failure, for in two cases of this work, where neither the number nor the size of the corpuscles was above normal, the viscosity values were still slightly raised above the normal limit. In this connection, the statement of Allbutt (2) may be mentioned that although the corpuscles have an important bearing on blood viscosity, the latter cannot be measured simply by the number and sizes of the corpuscles, as it depends to a certain extent also on the state of the plasma,

as, for example, on its colloid content.

Regarding the viscosity of the plasma, it may be mentioned that an increase in this alone would not necessarily cause an increase in viscosity of the whole blood, as the latter depends much more on the erythrocytes. Increase in plasma viscosity would nevertheless be an important additional factor, in so far as a smaller increase in number or size of the red cells, would, in the presence of increased viscosity of the plasma, probably be sufficient to bring about an increase in the viscosity of the whole blood.

Holker (71) has observed that the viscosity of the serum in syphilis is higher than normal, especially in the tertiary stage. Although it is interesting to note that the two cases above mentioned - where a relationship between blood viscosity and the number or size of the erythrocytes was not definitely established - were both cases of syphilitic aortic regurgitation, it is difficult to appreciate how increase in plasma viscosity alone could cause an increase in viscosity of the whole blood, a slight degree of which has apparently been present in these cases.

It is, however, reasonable to state in the light of Holker's observations, that where in cases of congestive heart failure due to syphilitic heart disease, some increase in number or size of the erythrocytes is present (even if, as in Case 45, this increase is only a moderate one), increase in viscosity of the plasma may be an important additional factor in raising the viscosity of the whole blood.

Hamburger (quoted by Sahli (121)) has elucidated the fact that *in vitro*, CO_2 in blood raises viscosity by increasing the size of the red cells, and it is generally agreed that - experimentally at least - besides increasing the colloid of the plasma, carbon dioxide in blood raises viscosity chiefly through its action in increasing the size of the red corpuscles. The mechanism of enlargement of the corpuscles - namely, the passage of anions and water into them from the plasma - has been described in an earlier section of the discussion.

The apparent relationship observed in this investigation between the increase in viscosity of the peripheral blood and the increase in size of the red cells, suggests that in congestive heart failure, where with increased venosity of blood in the tissues, the carbon dioxide pressure of the capillary and venous blood tends to be raised, a factor in the hyperviscosity is the increased CO_2, to which it is considered that the enlargement of the erythrocytes has been related. The importance of this factor *in vivo* will, however, depend on the extent of accumulation of CO_2 in the peripheral blood (controlled by the extent to which stasis occurs in the systemic capillaries), and also on the extent to which such accumulation is counteracted by elimination of CO_2 through the lungs, to which factors, as previously suggested, the enlargement of the corpuscles is related.

While, therefore, in some cases, the blood viscosity may be materially influenced by a significant enlargement of the red corpuscles above normal (apart from the effect of increase in

their number) in other cases where the erythrocytes exhibit a relatively smaller degree of enlargement, or are even normal in size, - due, it is considered, to relatively less accumulation of CO_2 - the importance of this factor may be proportionally less. In such cases, however, the viscosity may still be raised from the influence of increase in the number of red cells, which may explain the raised blood viscosity in Cases 42 and 56 of this investigation, where normal values for volume and diameter of the corpuscles were obtained.

It was noted, however, that the greater majority of cases exhibiting well-marked degrees of hyperviscosity - values for example ranging from 9.0 to 12.4 - showed significant increases in size of the erythrocytes above normal, as well as increases in their number, suggesting, in my opinion, that excess of CO_2 may frequently play an important part in the hyperviscosity of congestive heart failure through increasing the size of the red blood corpuscles.

While excess of CO_2 raises blood viscosity, which renders the blood stream sluggish, better aeration of the blood decreases it (121). Allbutt (2) states that this can be readily demonstrated by shaking blood in air, when a fall in viscosity is noted with oxidation. Allbutt further states that although on the mere mechanics of pulmonary respiration, it may not be always easy to explain the beneficial effect of oxygen inhalation in cardiac patients with cyanosis, nevertheless oxygen has a definite comforting effect on the patient, which he considers to be due probably to the fact that access of oxygen favours lessening of

the viscidity of the blood, with a consequent tendency for the blood stream to become less sluggish.

The observations in this work appear to indicate that a slight diminution in blood viscosity does in fact occur with inhalation of oxygen. The number and size of the red cells were both found to be increased above normal in the cases that were studied - namely, patients with severe congestive heart failure with well-marked secondary pulmonary lesions, - in some of whom pulmonary disease was present in addition to the heart failure - and the effect of oxygen was to cause, in each case, a slight reduction in erythrocyte count, and haemoglobin percentage, and also in volume and diameter of the individual red cells. It was mentioned in the analysis of the results that according to the standard of differences, the slight diminution in size of the cells occurring with oxygen inhalation should probably be disregarded. However, considering the fact that oxygenation of haemoglobin tends to drive out CO_2 from red corpuscles (74), it is considered that, in conjunction with the fall in the number of corpuscles (which confirms the observation of von Korányi (quoted by Allbutt (2)), a slight diminution has probably also occurred in their size, which has assisted in the reduction of the viscosity.

Regarding oxygen administration, Beaumont and Dodds (10) have pointed out that as a cardio-therapeutic measure, oxygen will only give relief if pulmonary lesions are present, and will not benefit symptoms due to circulatory stagnation. They state that oxygen should be used in cases of heart failure accompanied by arterial anoxaemia.

The patients of this investigation, in whom the effect of oxygen was studied, suffered, as previously stated, from pulmonary lesions, such as congestion and oedema, secondary to the heart failure, while three of them had in addition pulmonary disease, namely, chronic bronchitis and emphysema. Although the actual arterial oxygen saturation was not estimated, it may be considered that the relief in cyanosis and dyspnoea occurring with the administration of oxygen, has resulted from improvement in the accompanying condition of arterial anoxaemia. Although chiefly influencing arterial or anoxic anoxaemia, it is also possible that, by rendering the peripheral blood stream less sluggish, through the slight but consistent diminution in blood viscosity, the administration of oxygen tends to reduce peripheral stasis, and so improve, at least to a slight extent, the accompanying condition of stagnant anoxaemia.

While, however, reduction in blood viscosity with oxygen administration has only been relatively small, a greater reduction with usually a return to values within normal limits, has generally been exhibited in cases where removal of the heart failure occurred with rest in bed and therapeutic measures apart from oxygen, and has led to well-marked circulatory improvement. The greater reduction in viscosity in such cases was also associated with more marked diminution in the number of red cells (and in the percentage of haemoglobin) and also in the volume and diameter of the individual red cells.

These changes in the blood imply removal of the general

cellular oxygen want and carbon dioxide acidosis present in the tissues with circulatory failure and venous congestion, and the reduction in size and number of the erythrocytes no doubt materially assists in the lowering of the blood viscosity, as a result of which the blood stream is forwarded, the load on the heart is lessened, and a general improvement occurs in the patient.

A similar relief to the embarrassed and hindered circulation is no doubt effected by venesection, which was found to cause a fall in blood viscosity - to a slightly greater degree than that occurring with the administration of oxygen - associated with diminution in the number of red corpuscles and a slight diminution also in their size.

While a high blood viscosity is apparently frequently present in congestive heart failure, the results in this investigation show that it is also possible for the viscosity in congestive heart failure to be relatively lowered in some cases exhibiting general anasarca, where an associated relative diminution in the number of red cells and in haemoglobin percentage, suggests the presence of hydraemia. That under such conditions, the viscosity is relatively lowered is shown by the fact that a profuse diuresis, with subsidence of oedema, is in such cases followed by an apparently rapid rise in viscosity, together with a coincident increase in erythrocyte count and haemoglobin percentage.

Characteristically low values for blood viscosity were

obtained in cases of cardiac failure where infective endocarditis had supervened on chronic valvular disease. The low viscosity is probably related to the severe secondary anaemia associated with the bacterial toxins in the blood, which not only cause reduction of red cells and haemoglobin percentage, but apparently also affect the cell size, giving values below normal for both the volume index and the mean red cell diameter.

With regard to the exercise experiments, it was found that in three normal subjects, short violent exercise produced an increase in volume and diameter of the red cells, together with an increase in their numbers and in the haemoglobin percentage.

Increase in erythrocyte count and haemoglobin percentage after vigorous exertion has been noted by many observers, and has been put down, as indicated in the literature, to various causes, the principal being (i) concentration of blood from increased perspiration; (ii) liberation of additional corpuscles from the capillaries, and (iii) splenic contraction.

The rapid increases in erythrocyte count and haemoglobin percentage noted in the literature, have been confirmed by the exercise experiments in this work.

Regarding blood viscosity after violent exercise, which was not estimated in the present investigation, a rise is stated to occur by Sahli (121), due to excessive perspiration.

Increase in red cell diameter after violent exercise was

found to occur by Price-Jones (113), and Wiechmann and Schürmeyer (129), as previously stated, although this increase was doubted by Ponder and Saslow (110).

The results in the exercise experiments of this investigation for the size of the red cells, appear to confirm those of Price-Jones and Wiechmann and Schürmeyer, and in attempting to explain the increase that has apparently occurred, it is necessary, as in the case of cardiac failure, to study the physiological disturbances underlying severe exercise.

The three healthy subjects studied in this investigation all had a severe degree of breathlessness, together with palpitation, cardiac distress and exhaustion, at the conclusion of the exercise.

Meakins and Davies (95) state that such symptoms as dyspnoea, exhaustion, precordial discomfort, and even loss of consciousness, which result from the cellular oxygen want and carbon dioxide acidosis of circulatory failure due to cardiac disease, may be produced in health if muscular work is pushed to an extreme degree.

Cowan (25) states that the heart may fail before excessive physical work, and to quote Allan (3) .... "the uncomfortable symptoms present with a failing heart are the same as those produced by a healthy heart when subjected to a stress beyond the ordinary requirements of the body." Describing the breathlessness associated with exercise, McDowall (90) states that this can be considered as being due to a relative circulatory insufficiency, akin to that found in cardiac disease.

In violent exercise, considerable lactic acid and an excess

of carbonic acid are formed, and the pH of the plasma falls. The increase in alveolar CO_2 which is caused by violent exercise (133) suggests that under these conditions, an accumulation of CO_2 also occurs in the blood which is removed during the stage of hyperpnoea lasting for a short time at the end of the exercise. Campbell, Douglas and Hobson (21) have in fact concluded that during severe exercise, CO_2 is dammed back in the body, and according to Lovatt Evans (44) these observers have made it clear that coincident with increased pulmonary ventilation, "there is in all probability an increase both in carbon dioxide pressure and inferentially in the hydrogen ion concentration of the circulating blood."

Under the above conditions, the increase in size of the red cells found to occur in the blood of three normal subjects after violent exercise, when symptoms of severe circulatory embarrassment were present, may be reasonably regarded as analogous to the phenomenon observed in many cases of severe congestive heart failure.

SUMMARY AND CONCLUSIONS

The volume indices and mean diameters of the erythrocytes (between which a fairly close correspondence was found to exist), together with the number of the red cells, their individual haemoglobin content, and the haemoglobin percentage of the blood, have been studied in a series of 40 cases of congestive heart failure, due to a variety of lesions. In 24 of the cases, the viscosity of the blood was estimated, using the same viscosimeter - namely, the Hess instrument - for all the determinations. The findings in the cases of cardiac failure have been analysed and compared with average results obtained in a series of 12 normal individuals, and 20 cases of compensated heart disease, the viscosity results being compared with the average viscosity for 10 normal persons, and for eight of the compensated cases.

An attempt was made to produce symptoms of circulatory embarrassment in the normal subject, similar to those present in cardiac failure, by subjecting three normal individuals to violent exercise, consisting of standing-running as rapidly as possible, to exhaustion. The effect of violent exercise was studied on the size and number of the erythrocytes and the haemoglobin percentage. This work also includes a study of the effects of oxygen administration, venesection, and diuresis in congestive heart failure, on the number and size of the erythrocytes, and the viscosity of the blood.

(1) In fully compensated heart disease, the volume and diameter of the red blood cells show no variation from the normal. The number of erythrocytes is, on the average, also normal, likewise the haemoglobin percentage, and the haemoglobin content of the cells. The viscosity of the blood is within normal limits.

(2) In congestive heart failure, the volume index and mean diameter of the erythrocytes frequently exceed the normal. In most cases, a real and significant corpuscular enlargement is represented, but in a few cases, only a probable enlargement is present. The size of the erythrocytes may also be normal or subnormal.

(3) Generally speaking, the erythrocytes are larger than normal in severe congestive heart failure, and normal in cases where the failure is slight. This relationship between the degree of the failure and the size of the corpuscles is, however, not constant, as the latter may sometimes be normal or subnormal, when the symptoms of heart failure are severe.

(4) Enlargement of the erythrocytes has been found to occur in congestive heart failure secondary to mitral stenosis, mitral stenosis and regurgitation, aortic regurgitation with secondary mitral regurgitation, adherent pericardium, chronic bronchitis and emphysema, arterio-sclerosis, and chronic nephritis. In the cases of aortic regurgitation, however, corpuscular enlargement was usually greater when mitral

stenosis or chronic bronchitis and emphysema co-existed, than when failure of compensation occurred in pure aortic regurgitation.

(5) Smaller red cells than normal as described under (2) and (3) have only been found in cases of congestive heart failure associated with the cardiac type of infective endocarditis. The diminution in cell size is here attributed to the degenerative effect of bacterial toxins in the blood. In such cases estimation of volume index is more accurate than measurement of cell diameter, owing to the presence of poikilocytosis.

(6) Re-establishment of compensation in cases of cardiac failure with larger erythrocytes than normal, is associated with a return to normal cell volume and diameter, except possibly where the failure is secondary to emphysema and bronchitis, when slightly enlarged corpuscles may remain after circulatory improvement has occurred.

(7) A study of the colour index in relation to the size of the erythrocyte shows that enlargement of the latter in congestive heart failure is not associated with increase in its haemoglobin content. This affords evidence against the enlargement being analogous to that recorded by Vaquez in the cyanosis of congenital heart disease, where the haemoglobin content of the corpuscle was increased, and its enlargement was considered a compensation for anoxaemia.

(8) Evidence regarding enlargement of red cells occurring

experimentally in relation to CO_2 and blood reaction is described. It is suggested that increase in size of erythrocytes in the peripheral blood in congestive heart failure is a similar type of enlargement, occurring in respect of CO_2 accumulation and a tendency to acidaemia from circulatory stasis and insufficiency of elimination of CO_2 through the lungs, and depending on the degree of reduction in the circulation rate, and the extent of pathological changes in the lungs.

(9) Support is given to the above view by the fact that the corpuscular enlargement in congestive heart failure is frequently associated with the high red cell counts of peripheral stasis, and that it always occurs in the presence of the pulmonary lesions seen in severe congestive failure, apart from, in some cases, additional pulmonary disease, such as chronic bronchitis and emphysema.

(10) It is further suggested that the over-sized erythrocytes in the peripheral blood in congestive heart failure represent a phenomenon associated, in the light of known physico-chemical laws, with the transport by the cells of more CO_2, and an attempt generally to increase the buffering capacity of the blood.

(11) The red cell count in congestive heart failure may be increased, normal or diminished. It is usually increased - often to values between six and seven million red cells per cmm. - in severe cardiac failure (especially if cyanosis is marked), and normal or only slightly increased in mild cardiac failure. It may, however, be diminished in severe heart failure, from the

presence of (a) infection, (b) hydraemia, and (c) impairment of renal function, if sufficiently marked.

(12) As regards lesions, the erythrocyte count is found to be increased in severe congestive failure secondary to mitral valvular disease (especially mitral stenosis), adherent pericardium, chronic bronchitis and emphysema, arterio-sclerosis, and chronic interstitial nephritis, being higher in the two last-mentioned conditions, if pulmonary emphysema co-exists. The number of erythrocytes was not increased in a case of cardiac failure secondary to chronic parenchymatous nephritis, and showed a diminution with the increased degree of renal inadequacy, which was associated with increase in severity of the cardiac failure. In aortic regurgitation with failure of compensation, the count is not usually raised, unless emphysema and bronchitis co-exist, or the aortic lesion is combined with mitral stenosis. In cardiac failure associated with infective endocarditis, the red cell count is invariably diminished.

(13) Clinical improvement from congestive heart failure, when the latter has been associated with an increased red cell count, is characterised by a diminution in the number of erythrocytes. A normal count is usually obtained when compensation is re-established, but a raised count may tend to remain in patients with mitral stenosis or chronic bronchitis and emphysema, after circulatory improvement has occurred.

(14) This investigation confirms, from the evidence of diminished plasma volume obtained by the haematocrit, that the

increase in number of erythrocytes in the peripheral blood in congestive heart failure is in the nature of a relative polycythaemia.

(15) It is suggested that the high red cell counts in severe cases of congestive heart failure with marked cyanosis, may also represent an erythrocytosis, as a compensation for anoxaemia. The probable rôles played by the spleen and bone marrow in this connection have been discussed.

(16) The red cells in the peripheral blood in congestive heart failure show a lower average haemoglobin content than normal.

(17) This results chiefly from the fact that in the cases of cardiac failure with high red cell counts, the latter are proportionately more increased than are the haemoglobin percentages. With certain lesions, however, (e.g., infective endocarditis, aortic regurgitation, chronic parenchymatous nephritis), a low colour index in cardiac failure results from blood changes of a "secondary anaemia" type.

(18) Hydraemia, or dilution of the blood, is sometimes present in severe congestive heart failure, associated with gross oedema. It is characterised by a relative diminution in the number of erythrocytes and the haemoglobin percentage, both of which show a rapid and noticeable increase with subsidence of oedema following diuresis.

(19) Subsidence of oedema following diuresis in the cardiac hydraemia described above (18) is associated with a slight

diminution in volume and diameter of the red cells. The enlargement of the latter in the hydraemic stage, is, however, related more to the underlying circulatory failure than to the specific influence on the erythrocyte of the diluted character of the blood.

(20) The viscosity of the blood in congestive heart failure is in a great many cases higher than normal.

(21) Recovery from cardiac failure in such cases is associated with a fall in blood viscosity, which generally returns to values within normal limits.

(22) The increase of blood viscosity in congestive heart failure is in the great majority of cases related to increase in number or size of the red blood cells.

(23) Hyperviscosity in congestive heart failure is most marked when polycythaemia, and an increase above normal in the size of the erythrocytes, are both present, and reduction in viscosity with clinical improvement is, in such cases, associated with a coincident diminution in number and size of the cells.

(24) Venesection, and to a less extent, the administration of oxygen, lower the viscosity of the blood in congestive heart failure, in relation to a diminution in number and size of the erythrocytes. By lowering viscosity, such measures will tend to make the blood stream less sluggish, and help to relieve the embarrassed heart and circulation.

(25) The viscosity of the blood is relatively lowered in the presence of the hydraemia sometimes associated with gross

cardiac oedema. A rapid rise in viscosity occurs with subsidence of oedema following diuresis. These variations in viscosity are related to the associated diminution and increase respectively, in the number of red cells and the haemoglobin percentage, described under (18).

(26) A low blood viscosity characterises cardiac failure occurring in association with infective endocarditis.

(27) Violent exercise to exhaustion in the normal person, which is accompanied by circulatory and respiratory distress, causes a noticeable increase in red cell count and haemoglobin percentage, together with an increase in volume and diameter of the individual red cells. The possible causes of the polycythaemia are described, and it is suggested that the enlargement of the erythrocytes is analogous in character to that occurring in congestive heart failure.

I have to thank Dr. Harris, Physician to the Liverpool Heart Hospital, for placing patients in the wards and out-patient department at my disposal, and Dr. Lipkin, Biochemist to the Hospital, for the blood-urea estimations.

SUMMARY OF CASE REPORTS

Case 21. Male, aged 65; salesman. Heart failure, myocardial degeneration, arterio-sclerosis. No history of rheumatism or other etiological factors. Since 1927 complains of shortness of breath and pain in chest on slight exertion, occasional giddiness and swelling of ankles. For four weeks before admission, orthopnoea, swelling of legs and bad cough.

Admitted 4.2.29: orthopnoeic, dyspnoeic and cyanosed; frequent cough. Temperature 98.8° F. Heart: apical impulse diffuse, left border 5½" from mid-line in sixth space, no evidence of valvular disease, first sound at apex short and sharp, tic-tac rhythm, second aortic sound slightly accentuated, rate 120, regular. Electrocardiogram shows lesion of right bundle branch. Blood pressure 165/110 mm. Lungs: slight dullness at bases, numerous fine crepitations, respirations 32. Abdomen: liver enlarged, tender, no ascites. Considerable oedema of legs, slight pitting of thighs. Urine: S.G. 1024, albumin present, and a few hyaline casts. Radial arteries thickened and tortuous.

18.2.29. Condition still serious; cardiac signs as above, moderate oedema of legs. Albuminuria still present. Liver 2" below costal margin. Congestion and oedema both lung bases. Respirations 30; pulse-rate 110.

1.4.29. Considerably improved. Pulse-rate 78. Respirations 20. No dyspnoea or oedema. Liver not palpable, no albumin in urine. Still a cyanotic tinge of cheeks and a few râles at lung bases.

Discharged improved 6.4.29.

Case 22. Male, aged 58; Wallasey landing-stageman. Heart failure, myocardial degeneration, arterio-sclerosis, chronic interstitial nephritis. Shortness of breath on exertion and giddiness for a few years. Since October 1928, increasing dyspnoea, palpitations, swelling of feet and sometimes of face, and occasional attacks of nocturnal dyspnoea.

Admitted 11.3.29: orthopnoea, dyspnoea and fairly well-marked cyanosis, short, frequent cough. Temperature 98° F. Heart: apical impulse slightly thrusting, but diffuse, left border 6½" from mid-line in sixth space, soft systolic murmur at apex, aortic second sound slightly accentuated, rate 110, regular. Electrocardiogram: left ventricular preponderance, inversion of T in leads I and II. Blood pressure 180/130 mm. Lungs: a few rhonchi in front, dullness at bases, and numerous moist sounds heard, respirations 30. Abdomen: liver enlarged, tender, no ascites. Considerable oedema of feet and legs, and slight also of thighs and lumbar back. Urine: S.G. 1012, albumin present, hyaline and granular casts. Radial and retinal arteries thickened and tortuous, scattered retinal exudate. Blood urea 56.8 mg. per cent.

20.3.29. Condition still serious. Orthopnoea, marked dyspnoea and cyanosis. Marked oedema of legs and thighs, slight of back and face. Numerous moist râles heard at both lung bases. Pulse-rate 118, respirations 30. Urine: albumin present, also hyaline and granular casts.

7.5.29. Slight improvement. Orthopnoea and dyspnoea less

marked. Lung bases clearer. Liver smaller. Slight oedema of legs only. Pulse 94. Respirations 24.

21.6.29. Condition again serious. More dyspnoea and orthopnoea. Well-marked signs of congestion and oedema at lung bases. Oedema of legs, and lower part of thighs, slight of face. Liver increased in size, tender, slight ascites. Pulse 124. Respirations 34.

23.6.29. Worse. Drowsy and wandering at times. Blood urea 76 mg. per cent.

24.6.29. Died. No autopsy granted. Although towards the end, this patient showed renal symptoms and more urea retention, he was nevertheless clinically a case of congestive heart failure.

Case 23. Male, aged 67, foreman carter. Heart failure, myocardial degeneration, arterio-sclerosis, chronic bronchitis and emphysema. Occasional headaches, giddiness, and shortness of breath for about four years. 1925, acute bronchitis, and frequent exacerbations since. Since January 1929, orthopnoea, and swelling of legs.

Admitted 22.3.29: orthopnoeic, dyspnoeic, and cyanosed; cervical veins engorged, epigastric pulsation. Temperature 98° F. Heart: apex beat obscured, emphysema masks cardiac enlargement (sounds at apex heard best in sixth space 5½" to left of mid-sternum and about 1½" outside left border of deep cardiac dullness, as far as latter could be ascertained); systolic murmur at apex, second aortic sound accentuated, heart-rate 112, regular. Electrocardiogram: rather low voltage in all leads, inversion of T in lead II, and blurring of QRS deflection in leads II and III.

Blood pressure 170/110 mm. Lungs: emphysema, scattered rhonchi, numerous moist râles at both bases, respirations 30. Abdomen: liver enlarged, tender, no ascites. Oedema of legs and slight pitting of thighs. Urine: S.G. 1022, albumin present, a few hyaline and granular casts. Blood urea 35 mg. per cent. Radial and retinal arteries thickened, but no retinal haemorrhages or exudate seen.

27.4.29. Much improved. Dyspnoea and cyanosis slight. Liver much smaller, no ascites. Congestion of lung bases has cleared up. No oedema. No albumin in urine. Pulse rate 84. Respirations 20.

Discharged improved 1.5.29.

Case 24. Male, aged 38; ship's greaser. Heart failure, mitral stenosis (post-rheumatic), syphilitic aortic regurgitation. Rheumatic fever 1925. Dyspnoea and palpitation on exertion for some years, and occasional dull precordial pains. For a few weeks before admission, increasing disability with severe dyspnoea, troublesome cough, and swelling of feet.

Admitted 11.4.29: slight malar flush, prominence and pulsation of cervical veins, frequent cough with expectoration, occasionally blood-stained; orthopnoea, dyspnoea, and fairly well-marked cyanosis. Temperature 99° F. Heart: apical impulse diffuse, slightly forcible, left border 5½" from mid-line in sixth space, enlarged to right (deep cardiac dullness 1" to right of sternum), systolic and diastolic murmurs at mitral area, double aortic murmur, and soft tricuspid systolic murmur, rate 120,

regular. Blood pressure 135/45 mm. Lungs: dullness at both bases, impaired breath sounds, respirations 35. Abdomen: liver enlarged, and tender, slight ascites. Considerable oedema of feet and legs and pitting of lumbar back. Urine: S.G. 1028, albumin present, and a few hyaline casts. Wassermann reaction + +.

28.4.29. Died suddenly. Autopsy not granted.

Case 25. Female, aged 30; housewife. Heart failure, rheumatic heart disease, mitral stenosis, auricular fibrillation. History of chorea in 1919 and rheumatic fever in 1922. Swelling of ankles and dyspnoea and palpitation on slight exertion for two months before admission.

Admitted 11.4.29: mild degree of congestive failure, no orthopnoea, slight dyspnoea and cyanotic tinge of face and lips. Temperature 98·2° F. Heart: apical impulse slightly diffuse, left border 4½" from mid-line in fifth space, slightly enlarged to right (one finger's breadth dullness to right of sternum); mitral systolic and diastolic murmurs, auricular fibrillation, ventricular rate 110, radial pulse 94. Lungs: a few moist râles at bases after coughing, no dullness, respirations 24. Abdomen: liver slightly enlarged, no ascites. Oedema of ankles. Urine: S.G. 1020, trace of albumin.

Discharged 5.6.29, much improved.

Case 26. Female, aged 32; five children. Heart failure, rheumatic heart disease, mitral stenosis, auricular fibrillation. History of chorea at 16 years; shortness of breath and palpitation on exertion for past seven years. In 1924, induction of child, on account of heart condition; in 1926, lost power of right arm and leg, and speech - made complete recovery. For two months prior to admission, dyspnoea worse, palpitations, nausea and vomiting, swelling of legs and abdomen, and bad cough, with occasionally blood-stained sputum.

Admitted 13.4.29: cheeks flushed, pronounced pulsation in cervical veins; veins engorged, frequent cough; orthopnoea, marked dyspnoea and cyanosis. Temperature 98.6° F. Heart: apical impulse diffuse and feeble, left border $5\frac{1}{2}$" from mid-line in fifth space, enlarged to right (deep cardiac dullness $1\frac{1}{2}$" to right of sternum), systolic and diastolic murmurs at apex, auricular fibrillation; ventricular rate 150, radial pulse 120. Lungs: dullness at bases, impaired breath sounds, numerous fine crepitations, respirations 38. Abdomen: liver greatly enlarged, tender, ascites present. Oedema of legs, and lumbar back, and slight pitting of thighs. Urine: S.G. 1030, albumin present, a few hyaline casts.

Discharged herself, on 21.4.29, against hospital advice, still in serious condition.

Case 27. Female, aged 35; housewife, two children. Heart failure, rheumatic heart disease, mitral stenosis and regurgitation. History of chorea at 10 years, and rheumatic fever at 30 years,

breathlessness and palpitation on exertion for about 1½ years, becoming worse shortly before admission.

Admitted 13.4.29: mild cardiac failure; somewhat pale, with a malar flush, slightly dyspnoeic, not cyanosed. Temperature 98·6° F. Heart: moderately enlarged, left border 4¾" from mid-line in fifth space, apical impulse fairly forcible, presystolic thrill, systolic murmur at apex propagated into axilla, diastolic murmur to the right of apex with presystolic accentuation; rate 96, regular. Lungs: a few crepitations at bases, no dullness detected, respirations 22. Abdomen: liver slightly enlarged, no ascites. Slight oedema of legs. Urine: S.G. 1018, no albumin.

Discharged much improved 1.6.29.

Case 28. Female, aged 19; chocolate packer. Heart failure, rheumatic heart disease, mitral stenosis and regurgitation, aortic regurgitation. History of growing pains, and frequent tonsillitis, but not actually of rheumatic fever. In bed for some months before admission with increasing dyspnoea, cough, swelling of legs, back and abdomen.

Admitted 15.4.29: severe congestive heart failure. Malar flush, slightly icteric; orthopnoeic, extremely dyspnoeic and moderately cyanosed, pulsation of veins in neck, persistent cough. Temperature 98·6° F. Heart: apical impulse diffuse, and feeble, left border 6" from mid-line in sixth space, enlarged to right (deep dullness 1" beyond right sternal margin), diastolic

and blowing systolic murmurs at mitral area, (the latter audible at all other areas), aortic diastolic murmur conducted down the sternum, rate 126, regular. Blood pressure 112/55 mm. Lungs: signs of congestion and oedema both bases (dullness and many fine crepitations), respirations 38. Abdomen: liver palpable just below level of umbilicus, tender, ascites present; general anasarca present. Urine: S.G. 1027, albumin present, no casts seen.

26.4.29. Died. Autopsy not granted.

Case 29. Female, aged 48; housewife, three children. Heart failure, mitral stenosis and regurgitation. Only history is that of growing pains when a girl. Dyspnoea and palpitation on slight exertion for years. Since beginning of April 1929, dyspnoea at rest, increasing oedema and bad cough.

Admitted 23.4.29: malar flush, pulsation of cervical veins, orthopnoeic, dyspnoeic and slightly cyanosed. Temperature 97° F. Heart: apical impulse diffuse and feeble, left border 6" from mid-line in sixth space, moderately enlarged to right (deep dullness approx. 1" to right of sternum), presystolic thrill at apex, diastolic and blowing systolic murmurs at mitral area, the latter audible in axilla and at back, soft tricuspid systolic murmur, rate 120, regular. Lungs: dullness at bases, more marked at right base, where dullness was absolute, a right-sided hydrothorax being present; many moist sounds at left base, respirations 35. Abdomen: liver enlarged to level of umbilicus, tender, ascites present. Gross oedema of legs, thighs, and lower part of trunk,

and slight pitting of arms. Urine: S.G. 1028, albumin present and an occasional hyaline cast.

28.4.29. Slight improvement. Paracentesis has been performed for hydrothorax. Orthopnoea and dyspnoea slightly less marked. Oedema has greatly subsided following good response to digitalis and theobromine sodium salicylate.

15.5.29. Much improved. No dyspnoea at rest, slight cyanotic tinge of lips, no orthopnoea, and no oedema. Liver still palpable but much smaller, and not tender. Lungs practically clear. No albumin in urine. Pulse-rate 80. Respirations 20.

8.6.29. Discharged improved.

Case 30. Female, aged 60; housewife, ten children. Heart failure, chronic bronchitis and emphysema, auricular fibrillation. Breathlessness on exertion and recurrent winter cough for years; dyspnoea worse since 1928, orthopnoea being present at times. Increasing disability and unable to do any housework since February 1929.

Admitted 25.4.29: face congested, engorgement and pulsation of veins in marked neck, epigastric pulsation, orthopnoeic, extremely dyspnoeic and cyanosed. Temperature 98° F. Heart: impulse not felt, dullness cannot be detected owing to the well-marked emphysema, tricuspid systolic murmur audible over lower part of sternum, no other murmurs heard, auricular fibrillation; ventricular rate 140, radial pulse 120. Lungs: emphysema, rhonchi all over, scattered râles, numerous fine crepitations at both bases with impaired percussion note,

respirations 36. Abdomen: liver enlarged, tender, pulsating, no ascites. Oedema of feet and legs. Urine: S.G. 1026, albumin present, no casts seen.

23.5.29. Improved. No orthopnoea. Slight dyspnoea and cyanosis. No oedema. A few râles at lung bases, but latter generally much clearer. Respirations 24. Ventricular rate 80, no pulse deficit.

8.6.29. Discharged improved.

Case 31. Female, aged 37, four children. Heart failure, rheumatic heart disease, mitral stenosis, auricular fibrillation. Rheumatic fever at 10 years. Scarlet fever at 20 years. Dyspnoea and palpitation on slight exertion, and swelling of feet at times, for about six months before admission. For two weeks before admission, somewhat breathless at rest, and troubled with cough.

Admitted 13.4.29: moderate cardiac failure. Malar flush, slightly orthopnoeic and dyspnoeic, cyanotic tinge in cheeks and lips. Temperature 97·6° F. Heart: apical impulse slightly diffuse, left border 4¾" from mid-line in fifth space, moderately enlarged to right (deep cardiac dullness 1" to right of sternum), systolic and diastolic murmurs at mitral area, auricular fibrillation, ventricular rate 120, radial pulse 102. Lungs: a few rhonchi in front, and a few râles at bases, respirations 24. Abdomen: liver slightly enlarged, no ascites. Slight oedema of legs. Urine: S.G. 1022, trace of albumin.

26.4.29. Condition improving with digitalis, but there are still signs of slight congestive failure. Liver slightly enlarged, and some oedema still present in legs. A few crepitations are heard at base of right lung. Ventricular rate 100, radial pulse 88. Respirations 22.

Discharged much improved 15.6.29.

Case 32. Female, aged 39; housewife, six children, no miscarriages. Heart failure, exophthalmic goitre, auricular fibrillation. No history of rheumatism. Swelling of throat, breathlessness and palpitation, and exhaustion since 1925. Loss of weight since 1927. For a few weeks before admission, dyspnoea and palpitation on slight exertion.

Admitted 13.6.29: mild degree of congestive failure; slightly dyspnoeic, but not cyanosed. Clinical signs of exophthalmic goitre. Heart: apical impulse fairly diffuse, left border 5" from mid-line in sixth space, systolic bruit heard at all areas, auricular fibrillation, ventricular rate 110, radial pulse 96. Lungs: a few crackles at bases, no dullness, respirations 22. Abdomen: liver slightly enlarged, no ascites. Slight oedema of legs. Urine: S.G. 1016, trace of albumin.

Discharged improved 1.8.29.

Case 33. Female, aged 25; housewife, no children. Heart failure, syphilitic heart disease, aortic regurgitation. No history of rheumatism. Precordial pain and dyspnoea on exertion since 1926, and occasional giddiness. Increasing dyspnoea for four weeks before admission, also swelling of feet, cough and general weakness.

Admitted 17.6.29: somewhat pale with cyanotic tinge of cheeks, moderately orthopnoeic, and dyspnoeic. Temperature 98° F. Heart: apical impulse moderately forcible, but diffuse, left border 5" from mid-line in sixth space, aortic systolic and diastolic murmurs, mitral systolic murmur propagated towards axilla, rate 100, regular. Electrocardiogram: left ventricular preponderance, slight increase in P-R interval. Blood pressure 130/50 mm. Lungs: slightly impaired breath sounds at bases, and fine moist râles heard, respirations 26. Abdomen: liver enlarged, (1½" below costal margin) no ascites. Oedema of feet and slight of legs. Urine: S.G. 1020, trace of albumin. Wassermann reaction positive (++).

Discharged at own request, 26.6.29.

Case 34. Male, aged 21; butcher. Heart failure, rheumatic heart disease, mitral stenosis, auricular fibrillation. Rheumatic fever at seven years and frequent attacks of tonsillitis. Dyspnoea on exertion for a few years, much worse since May 1929, and associated with palpitations, cough and increasing disability. Swelling of legs and abdomen for two weeks before admission and vomiting for three days.

Admitted 19.6.29; extreme congestive heart failure, almost moribund. Orthopnoeic, dyspnoeic and cyanosed (the cyanosis being associated with jaundice and giving face dusky-green tint). Marked venous pulsation in neck. Frequent cough. Temperature 97° F. Heart: apical impulse diffuse and feeble, left border 5¼" from midline in fifth space, enlarged to right (deep cardiac dullness 2" to right of sternum), systolic and diastolic murmurs at apex, auricular fibrillation, ventricular rate 160, radial pulse not palpable. Lungs: rhonchi in front, numerous fine moist râles at both bases, with dullness, and impaired breath sounds, respirations 36. Abdomen: liver enlarged to level of umbilicus, tender, pulsating, ascites present. General anasarca present. Urine: S.G. 1026, albumin present, no casts seen.

Died 12 hours later. No autopsy granted.

Case 35. Male, aged 50; contractor. Heart failure, myocardial degeneration, arterio-sclerosis, chronic interstitial nephritis. Since 1926, headaches, dizziness, breathlessness and occasional precordial pain on exertion, slight swelling of ankles at night, dyspeptic symptoms, and fairly frequent bronchitis. Since May 1929, dyspnoea on slightest exertion, often nocturnal, and at times, orthopnoea.

Admitted 2.7.29; high coloured, orthopnoeic, markedly dyspnoeic and cyanosed, engorgement of cervical veins. Temperature 98.2° F. Heart: apex beat impalpable, and cardiac dullness cannot be definitely detected owing to co-existing well-marked emphysema, apex position as determined by auscultation, 6" to left of mid-sternum in sixth space, rough systolic murmur at apex, second

aortic sound accentuated, rate 100, regular. Electrocardiogram: left ventricular preponderance, QRS bizarre in leads II and III, inversion of T in lead II. Blood pressure 200/135 mm. Lungs: emphysema, scattered sibilant rhonchi, numerous moist râles at both bases, where percussion note was impaired, respirations 28. Abdomen: liver enlarged, tender, no ascites. Oedema of legs and slight pitting of thighs. Urine: S.G. 1014, slight albumin, a few hyaline and granular casts. Radial arteries thickened and tortuous. Flame-shaped haemorrhages in retina, and scattered white exudates. Blood urea 60 mg. per cent.

3.7.29. Dyspnoea and cyanosed relieved after oxygen administration.

20.7.29. Has improved under treatment. Orthopnoea, but little dyspnoea, cyanosis slight. No oedema. Liver just palpable. No crepitations at lung bases. Pulse 80. Respirations 20.

24.7.29. Discharged at own request, for further rest at home.

Case 36. Female, aged 66; two children, and one miscarriage. Heart failure, syphilitic heart disease, aortic regurgitation; dyspnoea on slight exertion for about 12 months, and dull, precordial pains, occasional swelling of feet and increasing disability.

Admitted 18.7.29; pale, slight cyanosis, moderate orthopnoea, and dyspnoea; venous pulsation observed in neck. Temperature 97.6° F. Heart: apical impulse diffuse, and feeble, left border 6½" from mid-line in sixth space, slight dullness (about one

finger's breadth) detected to right of sternum at level of fourth rib, aortic diastolic murmur conducted down sternum, mitral systolic murmur propagated towards axilla, and soft systolic murmur audible in tricuspid area, rate 110, regular. Blood pressure 160/55 mm. Electrocardiogram suggestive of an arborisation block, from the ventricular complexes. Lungs: impaired breath sounds and fine moist râles at both bases, respirations 30. Abdomen: liver enlarged and tender, no ascites. Oedema of legs. Urine: S.G. 1022, albumin present, no casts seen. Wassermann reaction positive (++).

22.7.29. Slight improvement. Dyspnoea less. Pulse 96. Respirations 26.

29.7.29. Condition has deteriorated. More dyspnoeic and orthopnoeic. Numerous râles at lung bases; liver increased in size; more oedema of legs, slight pitting of thighs. Pulse 120, respirations 34.

31.7.29. Worse, dying; cyanosis more marked to-day.

1.8.29. Died. Autopsy not granted.

Case 37. Female, aged 36; waitress, single. Heart failure, myocardial degeneration, chronic parenchymatous nephritis. Acute nephritis 1924. Since then, dyspnoea and palpitation on exertion; dyspeptic symptoms, headaches, dizziness, loss of weight and occasional swelling of ankles. Since April 1929, increasing dyspnoea, and swelling of legs, also cough and exhaustion.

Admitted 25.7.29. Pale, slight cyanosis, orthopnoea.

Temperature 98° F. Heart: impulse diffuse, left border 5¼" from mid-line in sixth space, second aortic sound accentuated, mitral systolic murmur conducted to axilla, rate 114, regular. Blood pressure 168/110 mm. Electrocardiogram: left ventricular preponderance, inversion of T in lead II. Lungs: a few rhonchi in front, dullness at bases and numerous fine crepitations heard, respirations 28. Abdomen: liver slightly enlarged (1" below costal margin) no ascites. Oedema of legs and slight pitting of thighs. Albuminuric retinitis. Urine: S.G. 1024, albumin present; leucocytes, hyaline and occasional finely granular casts. Blood urea 72 mg. per cent.

19.9.29. Condition worse. Marked dyspnoea and orthopnoea. Pulsation in cervical veins. Liver three fingers' breadth below costal margin and tender. Heart enlarged to right, as well as to left (deep cardiac dullness 1" to right of sternum), all sounds soft. Numerous moist râles at lung bases. Oedema as before with slight pitting of lumbar back. Pulse 128, regular. Respirations 34. Inclined to be drowsy and wandering at times. Blood urea 124 mg. per cent.

28.9.29. Died. Autopsy not granted. This patient was clinically a case of heart failure, although near the end, she showed renal symptoms and much more urea retention.

Case 38. Male, aged 49; steward. Heart failure, chronic bronchitis and emphysema, auricular fibrillation. Bronchitis each winter since 1920. Dyspnoea on exertion for some years;

increasing in severity since February 1929, and since then orthopnoea at times, and more or less constant cough. Swelling of feet and ankles, and palpitations for two months before admission.

Admitted 2.8.29; deeply cyanosed; orthopnoeic, and extremely dyspnoeic. Engorgement and pulsation of veins in neck. Well-marked epigastric pulsation. Temperature 98.4° F. Heart: apex beat not felt, no cardiac dullness detected on account of the marked emphysema, soft tricuspid systolic murmur over lower sternum, no other murmurs heard, auricular fibrillation, ventricular rate 130, radial pulse 110, (this patient's electrocardiogram showed normal rhythm when he attended the Out-Patient Department in July 1927). Lungs: respirations 30, well-marked signs of emphysema, rhonchi heard all over, scattered râles, numerous at both bases. Abdomen: liver enlarged, tender, ascites present. Oedema of feet and legs, and slight pitting of thighs. Urine: S.G. 1030, albumin present, and a few hyaline casts. Radial arteries not thickened.

Transferred to another hospital 22.11.29, condition improved.

Case 39. Male, aged 31; rigger. Heart failure, syphilitic heart disease, aortic regurgitation. Dyspnoea and palpitation on exertion for two years, also giddiness, and occasional substernal pain. Dyspnoea more severe since March 1929 and unable to work since. Swelling of legs and bad cough shortly before admission.

Admitted 30.8.29; pale, orthopnoeic, dyspnoeic and slightly cyanosed; frequent cough. Temperature 98.4° F. Heart: impulse diffuse, left border 5½" from mid-line in sixth space, systolic and diastolic murmurs originating in aortic area (no basal thrill), mitral systolic murmur propagated to axilla, and slight systolic murmur in tricuspid area, rate 100, regular. Electrocardiogram: inverted T in lead I; left ventricular preponderance. Blood pressure 145/50 mm. Lungs: scattered rhonchi, numerous, fine crepitations at both bases, where percussion note impaired; respirations 32. Abdomen: liver enlarged, tender, slight ascites present. Gross oedema of legs, thighs and lumbar back, pitting of abdominal wall and slightly of arms. Urine: S.G. 1026, albumin present, no casts seen. Wassermann reaction ++.

2.9.29. Slightly improved. Subsidence of oedema, following diuresis up to 100 oz. in past 24 hours from intramuscular injection of 0.75 cc. novasurol. Pulse 96, respirations 26.

Discharged himself home on 2.10.29 (condition improved).

25.10.29. Readmitted, with recurrence of congestive heart failure. Orthopnoeic, dyspnoeic and moderately cyanosed, heart enlarged, congestion and oedema both lung bases. Considerable oedema of legs and thighs, slight "lumber pad", enlarged, tender liver. Urine contains albumin. Temperature 98.6° F. Pulse rate 120, respirations 32.

4.11.29. Slight improvement. Dyspnoea less; oedema diminished following diuresis up to 89 oz. in past 24 hours.

14.11.29. Continued improvement. No dyspnoea or cyanosis.

Liver slightly palpable, not tender. Lung bases much clearer, oedema of ankles only. No albumin in urine. Pulse 84. Respirations 22.

16.11.29. Discharged at own request, for further rest at home, his condition being generally much improved.

Case 40. Male, aged 69; no occupation. Heart failure, syphilitic heart disease, aortic regurgitation; myocardial degeneration. Typhoid fever at 32 years. Since 1924, dyspnoea and palpitation on exertion, giddiness and attacks of precordial pain. Since July 1929, swelling of feet, cough, and general exhaustion.

Admitted 13.9.29; pale, orthopnoeic, dyspnoeic and slightly cyanosed, pulsation of cervical veins. Temperature 98° F. Heart: apical impulse diffuse and feeble, left border 6½" from mid-line in sixth space, slight enlargement to right (deep dullness ½" - 1" to right of sternum), mitral systolic murmur, aortic systolic and diastolic murmurs, and a tricuspid systolic murmur also audible, rate 110, regular. Electrocardiogram shows right bundle branch block. Blood pressure 140/45. Lungs: slight dullness at bases, moist sounds present, respirations 28. Abdomen: liver enlarged, slightly tender, no ascites. Oedema of feet and legs. Urine: S.G. 1022, albumin present, no casts seen. Wassermann reaction ++.

9.10.29. Condition practically unchanged. Orthopnoea, enlarged liver, oedema of legs, râles at lung bases. Pulse 116. Respirations 30. Extra-systoles present.

Discharged himself against hospital advice 27.11.29, still in serious condition.

Died shortly afterwards at home.

Case 41. Female, aged 28; housewife, no children. Heart failure, rheumatic heart disease, mitral stenosis, auricular fibrillation. Rheumatic fever at 16 years; dyspnoea on exertion since January 1929, swelling of ankles, and since then increasing dyspnoea, and palpitations, and bad cough, with occasionally blood-stained sputum. Unable to do any housework since August 1929.

Admitted 23.9.29; malar flush, orthopnoea, marked dyspnoea and cyanosis; frequent cough. Engorgement and pulsation of veins in neck. Temperature 98.4° F. Heart: apical impulse diffuse, left border 5" from mid-line in fifth space, enlarged to right (deep cardiac dullness 2" to right of sternum), mitral systolic and diastolic murmurs, also soft systolic murmur in tricuspid area, auricular fibrillation, ventricular rate 140, radial pulse 120. Lungs: dullness at both bases, impaired breath sounds, and numerous fine crepitations, respirations 32. Abdomen: liver enlarged, tender, pulsating, ascites present. Oedema of feet and legs, slight pitting of thighs. Urine: S.G. 1028, albumin present, no casts seen.

24.9.29. Dyspnoea and cyanosis relieved after oxygen administration.

27.11.29. Considerable improvement. No orthopnoea or dyspnoea, cyanotic tinge of cheeks and lips. Lung bases clear. No

oedema. Liver not palpable. No albumin in urine. Respirations 20. Ventricular rate 70, no pulse deficit.

30.11.29. Discharged much improved.

Case 42. Female, aged 48; housewife, two children. Heart failure, rheumatic heart disease, mitral stenosis, auricular fibrillation. Rheumatic fever at 23 years and dyspnoea on exertion practically ever since. In 1928, had a left sided hemiplegia from which she recovered. Since July 1929 dyspnoea worse, palpitations and swelling of legs.

Admitted 25.9.29; slight malar flush; orthopnoeic, moderately dyspnoeic and cyanosed. Pulsation of cervical veins. Temperature 97.6° F. Heart: impulse diffuse, left border 5" from mid-line in fifth space, enlarged to right (deep cardiac dullness 1½" to right of sternum), mitral systolic and diastolic murmurs, soft tricuspid systolic murmur, auricular fibrillation, ventricular rate 120, radial pulse 100. Lungs: a few moist râles at bases and slightly impaired breath sounds, respirations 26. Abdomen: liver enlarged, tender, no ascites. Moderate oedema of legs. Urine: S.G. 1024, slight albumin, no casts.

28.9.29. Patient declined to remain in hospital and discharged herself, still in fairly serious condition. Subsequent history not known.

Case 43. Female, aged 38; housewife. Heart failure, rheumatic heart disease, mitral stenosis and regurgitation,

auricular fibrillation. Rheumatic fever at 13 years. Subject to occasional attacks of bronchitis since. Dyspnoea on exertion for some years. In 1926, attended Out-Patient Department of Liverpool Heart Hospital, and diagnosed as mitral stenosis and regurgitation (normal rhythm present at that time). Since July 1929, dyspnoea more severe, palpitations, exhaustion, swelling of ankles and bad cough.

Admitted 27.9.29; malar flush, orthopnoeic, dyspnoeic and moderately cyanosed; pulsation in cervical veins. Temperature 98° F. Heart: impulse diffuse, left border 6" from mid-line in sixth space, enlarged to right (deep cardiac dullness 1½" to right of sternum), systolic and diastolic murmurs at apex, the former being propagated well into axilla, and audible at all other areas, auricular fibrillation, ventricular rate 130, radial pulse 100. Lungs: a few rhonchi in front, dullness and fine moist râles at both bases, respirations 30. Abdomen: liver enlarged, tender, no ascites. Oedema of feet and legs. Urine: S.G. 1024, albumin present, no casts.

22.10.29. Considerably improved. Ventricular rate 72, no pulse deficit. Respirations 18, lung bases clear. No dyspnoea, cyanosis, or pulsation of veins in neck; liver just palpable. No oedema, and no albumin in urine.

15.11.29. Discharged improved.

Case 44. Male, aged 58; no occupation. Heart failure, rheumatic heart disease, mitral stenosis, aortic regurgitation, chronic bronchitis and emphysema. Rheumatic fever at 28 years

and "heart trouble" since. Bronchitis each winter since 1920. Complaining of shortness of breath and palpitation on exertion, and occasional giddiness for a few years, worse since June 1929, when exhaustion and swelling of legs developed.

Admitted 7.10.29; orthopnoea, marked dyspnoea and cyanosis. Engorgement and pulsation of veins in neck. Well-marked epigastric pulsation. Temperature 98.4° F. Heart: apex beat impalpable, no cardiac dullness made out owing to well-marked emphysema, presystolic and systolic murmurs at apex, latter audible at all other areas and in axilla, aortic diastolic murmur conducted down sternum, heart sounds faint, rate 114, regular. Blood pressure 140/65 mm. Lungs: emphysema, scattered rhonchi, and râles, numerous crepitations at both bases, respirations 32. Abdomen: liver enlarged, and tender, ascites present. Oedema of feet and legs. Urine: S.G. 1025, albumin present, a few hyaline casts. Wassermann reaction negative.

8.10.29. Dyspnoea and cyanosis less after oxygen administration.

11.10.29. Condition worse. Died to-day. Autopsy: Lungs large and emphysematous, both bases congested and oedematous. Cardiac hypertrophy and dilatation. Aortic valve sclerotic and calcareous, opening stenosed and incompetent. Patchy atheroma of lower aorta. Calcareous plaque at edge of one coronary artery, but both vessels patent throughout course. Mitral valve thickened, stenosed and incompetent. Tricuspid orifice enlarged. "Nutmeg" liver. Spleen shows venous congestion. Kidneys show early arterio-sclerotic changes, and venous congestion, latter more marked in right.

Case 45. Male, aged 53; painter. Heart failure, syphilitic aortic regurgitation; chronic bronchitis and emphysema. History of bronchitis since 1914 - pensioned for bronchitis - also giddiness, shortness of breath on exertion. Shortly before admission became dyspnoeic at rest, and feet and legs became swollen.

Admitted 11.11.29; orthopnoea, marked dyspnoea and cyanosis; engorgement and pulsation of cervical veins, well-marked epigastric pulsation. Temperature 99° F. Heart: apex beat obscured by emphysema, but its position, as determined by auscultation, is in sixth space, 6" to left of mid-sternum, mitral systolic murmur propagated to axilla, double aortic "to-and-fro" murmur, soft tricuspid systolic murmur, rate 100, regular. Blood pressure 130/60 mm. Lungs: emphysema, rhonchi all over, scattered râles, numerous at both bases, respirations 28. Abdomen: liver enlarged, tender, no ascites. Oedema of feet and legs, and slight of back. Urine: S.G. 1024, albumin present, no casts seen. Wassermann reaction ++.

15.11.29. Transferred to another hospital.

Case 46. Male, aged 60; cold storage worker. Heart failure, chronic bronchitis and emphysema. Bronchitis each winter since 1919 - severe attack past winter. Dyspnoea on exertion for some years, and more or less constant since beginning of 1929. Since September 1929, oedema of feet and palpitations.

Admitted 14.11.29; high coloured, venous pulsation and engorgement in neck. External veins of chest dilated. Well-marked epigastric pulsation. Orthopnoeic, extremely dyspnoeic and cyanosed. Temperature 97° F.

Heart: apical impulse obscured, cardiac dullness absent, on account of the marked emphysema, heart sounds faint, soft tricuspid regurgitant murmur audible over lower part of sternum, no other murmurs heard, rate 112, regular. Blood pressure 138/86 mm. Lungs: well-marked signs of emphysema, rhonchi all over, and scattered râles; fine crepitations at both bases, where percussion note was impaired, respirations 32. Abdomen: liver enlarged, pulsating, no ascites. Considerable oedema of legs, slight pitting of thighs. Urine: S.G. 1026, albumin present, no casts seen. Radial arteries not thickened.

20.11.29. Relief in dyspnoea, and cyanosis less marked, following oxygen inhalations.

21.11.29. Died. No autopsy.

Case 47. Female, aged 24; pianist. Heart failure, rheumatic heart disease, mitral stenosis, and regurgitation, auricular fibrillation. History of tonsillitis, growing pains and "heart disease" at ten years, and since then, shortness of breath on exertion. Since July 1929, dyspnoea more pronounced, also palpitations, bad cough, and increasing oedema.

Admitted 25.11.29; malar flush, orthopnoeic, dyspnoeic and cyanosed; persistent cough, marked venous pulsation in neck. Temperature 98.6° F. Heart: apical impulse diffuse, left border 5½" from mid-line in sixth space, enlarged to right (deep cardiac dullness 1¾" to right of sternum), mitral systolic and diastolic murmurs present, (the systolic murmur being fairly loud and heard

at all other areas), auricular fibrillation, ventricular rate 160, radial pulse 120. Lungs: dullness at both bases, diminished breath sounds, and large number of moist râles present, respirations 34. Abdomen: liver enlarged, tender, ascites present. Considerable oedema of legs, and slightly also of thighs and lumbar back. Urine: S.G. 1030, albumin present, and an occasional hyaline cast.

1.12.29. Condition practically unchanged, but oedema less marked and breathing less laboured. Ventricular rate 120. Radial pulse 100. Respirations 30.

1.1.30. Improved. No orthopnoea, but still slightly dyspnoeic, and slightly cyanosed. Liver smaller, no ascites. Slight oedema of legs. Respirations 24. Ventricular rate 88, no pulse deficit.

19.1.30. Considerably improved. No dyspnoea, slight cyanotic tinge of lips. No engorgement of cervical veins. No oedema. Liver just palpable. Heart rate 78, no pulse deficit. Respirations 20.

22.1.30. Discharged improved.

Subsequent history. Readmitted to Liverpool Heart Hospital on 15.10.30, with recurrence of gross congestive failure, and eventually died on 19.1.31. Autopsy granted, and principal findings were :- Heart: general hypertrophy and dilatation; wall of left auricle showed irregular areas of thickened endocardium and there were recent, small, nodular vegetations on the mitral, aortic and pulmonary valve flaps. Mitral valve stenosed and

incompetent. Tricuspid orifice enlarged. Nutmeg liver, and venous congestion also of spleen. Capsule of each kidney stripped easily, cortex looked normal and medulla congested. Right kidney larger than left.

A pathological report on the post-mortem material of this case was received from Professor J. M. Beattie, Honorary Pathologist and Bacteriologist to the Liverpool Heart Hospital, who discovered two points of special interest. These were as follows :-

(1) Heart: Left auricle showed, naked eye, irregular areas of thickening of endocardium. These were well seen in section and were newly formed fibrous tissue. The fibroblasts were well marked, and other cells scanty in superficial areas.

(2) Spleen: Marked congestion of pulp sinuses. The arteries in the Malpighian bodies had thickened walls and in a few, the new fibrous tissue was hyaline. Scattered through the organ were small masses of a Gram-positive coccus; they were so massed - forming plugs in some vessels - that it was difficult to define them. Professor Beattie's view was that they were streptococci rather than staphylococci.

Summing up the report, Professor Beattie states that the whole condition suggested pathological changes associated with a chronic heart condition, the interesting points being the presence of organisms in the spleen (not found in any other organ) and the thickened patches on the endocardium of the auricle.

Case 48. Female, aged 33; housewife. Heart failure, rheumatic heart disease, mitral stenosis and regurgitation. No history of rheumatic fever, but history of growing pains. Scarlet fever at 14 years. Dyspnoea and palpitation on exertion for some years. During 1927, was an in-patient in Liverpool Heart Hospital, with mild congestive failure. Since then, has kept fairly well, but following an attack of bronchitis two months before admission, the dyspnoea became worse, swelling of the legs developed, and she has been unable to do any housework.

Admitted 29.11.29. Cheeks flushed, engorgement of veins in neck; orthopnoeic, dyspnoeic and moderately cyanosed. Temperature 97° F. Heart: apical impulse diffuse, left border $6\frac{1}{2}$" from midline in sixth space, enlarged to right (deep cardiac dullness $1\frac{1}{2}$" to right of sternum), presystolic thrill at apex, presystolic and systolic mitral murmurs, the latter audible at all other areas, in axilla, and at back, rate 120, regular. Lungs: fairly numerous rhonchi, dullness at bases, impaired breath sounds, and large number of fine crepitations, respirations 34. Abdomen: liver enlarged, slightly tender, no ascites. Oedema of legs and lumbar back. Urine: S.G. 1025, trace of albumin, no casts seen.

12.1.30. Considerably improved, practically no signs of heart failure. No dyspnoea at rest, slight cyanotic tinge of lips, no engorgement of veins in neck. Bases of lungs clear. Liver slightly palpable, but not tender. No oedema. No albumin in urine. Pulse rate 80, Respirations 20.

Discharged improved 18.1.30.

Case 49. Female, aged 60; housewife. Heart failure, myocardial degeneration, arterio-sclerosis, aortic regurgitation. Diphtheria at 30 years, no other diseases. Complains of shortness of breath and palpitation on exertion, precordial pain, giddiness and occasional faintness for some years. Since July 1929, dyspnoea and palpitation more marked, increasing exhaustion and swelling of feet and ankles towards evening.

Admitted 6.1.30; orthopnoeic, dyspnoeic, and moderately cyanosed; engorgement of veins in neck. Heart: apical impulse diffuse, slightly forcible, left border $6\frac{1}{2}$" from mid-line in sixth space, one finger's breadth of deep cardiac dullness detected to right of sternum, aortic systolic and diastolic murmurs, systolic murmur at apex, propagated to axilla, rate 104, regular. Blood pressure: 180/70 mm. Electrocardiogram: Left ventricular preponderance; inversion of T in leads I and II. Lungs: dullness at both bases, and numerous fine crepitations heard, respirations 28. Abdomen: liver 2" below costal margin, tender, no ascites. Oedema of legs. Urine: S.G. 1024, albumin present and an occasional hyaline cast. Radial artery irregularly thickened. Wassermann reaction negative.

7.2.30. Considerably improved. Slight dyspnoea on exertion, no cyanosis. Lungs clear. No oedema or albuminuria. Pulse 76. Respirations 20.

12.2.30. Discharged improved.

Case 50. Female, aged 21; theatre attendant. Heart failure, infective endocarditis, rheumatic heart disease, mitral stenosis and regurgitation, aortic regurgitation. Rheumatic fever at 14 years. History of increasing shortness of breath and palpitation on exertion; weakness and exhaustion for about three years, worse for three months before admission, and associated with cough, and swelling of legs.

Admitted 17.12.29: pale, thin, moderately dyspnoeic; no cyanosis. Temperature 100·2° F. Heart: impulse diffuse and weak, left border 6" from mid-line in sixth space, moderately enlarged to right (deep cardiac dullness 1" to right of sternum), presystolic and systolic mitral murmurs (the latter loud and heard at all other areas), and a well-marked blowing aortic diastolic murmur present and conducted down sternum, rate 114, regular. Blood pressure 110/40 mm. Lungs: impaired breath sounds, and fine moist râles at bases, respirations 28. Abdomen: liver and spleen enlarged, no ascites. Oedema of feet and ankles. Urine: S.G. 1022, trace of albumin, and a few red blood cells. Wassermann reaction negative.

15.1.30. Condition of cardiac failure practically as above, dyspnoea, orthopnoea, râles at bases of lungs, hepatic and splenic enlargement, and oedema of legs. Blood culture positive, streptococci being present. Temperature 100° F. Pulse 112. Respirations 26.

21.2.30. Condition unchanged. Temperature 100° F. Pulse 120. Respirations 30.

1.3.30. Discharged, at own request. Died shortly afterwards at home.

Case 51. Female, aged 14; schoolgirl. Heart failure, rheumatic heart disease, mitral stenosis and regurgitation. Rheumatic fever in 1926 and chorea in 1927, and shortness of breath on exertion since. Since September 1929, increasing dyspnoea, with palpitations, cough and swelling of feet and legs, and dyspepsia.

Admitted 20.1.30: malar flush, engorgement and pulsation of cervical veins, cyanosed, orthopnoeic and dyspnoeic, persistent cough. Temperature 99° F. Heart: impulse diffuse, left border 5½" from mid-line in sixth space, enlarged to right (deep cardiac dullness 1½" to right of sternum) presystolic thrill at apex, first sound loud and slapping at mitral area, second pulmonic sound accentuated, diastolic and systolic murmurs at mitral area, the latter murmur being audible at all other areas, and in axilla, rate 124, regular. Lungs: scattered rhonchi, dullness at both bases, deficient breath sounds and numerous fine crepitations, respirations 32. Abdomen: liver enlarged, tender, ascites present. Considerable oedema of legs, and slight pitting of thighs. Urine: S.G. 1026, albumin present, no casts seen.

25.2.30. Condition very serious. Orthopnoeic and very dyspnoeic, with well-marked signs of congestion and oedema at lung bases. General anasarca now present, and a diminished urinary output (18 oz. in past 24 hours). Right-sided hydrothorax present.

Pulse 130. Respirations 38.

26.2.30. Patient feels easier. Prompt diuresis up to 100 oz. in past 24 hours following intramuscular injection of 1 cc. novasurol on 25.2.30, and dyspnoea relieved after paracentesis thoracis.

This patient maintained a slight improvement after this, but a week later (on 6.3.30) she suddenly became unconscious and died (? cerebral embolism). Autopsy not granted.

Case 52. Male, aged 31; diver's linesman. Heart failure, infective endocarditis, rheumatic heart disease, mitral stenosis and regurgitation, aortic regurgitation. Rheumatic fever at 11 years; and history of growing pains. Malaria three times in Sierra Leone. History of shortness of breath and palpitation on slight exertion for about five months before admission, worse since December 1929, and associated with bad cough, swelling of feet and increasing weakness.

Admitted 5.2.30: pale, orthopnoea, and dyspnoea, no cyanosis, pulsation in cervical veins. Temperature 101° F. Heart: impulse diffuse, and weak, left border 5½" from mid-line in sixth space, enlarged to right (deep heart dullness extends slightly over 1" to right of sternum), presystolic and systolic mitral murmurs, (latter propagated into axilla and audible at all other areas), aortic diastolic murmur conducted down sternum, systolic murmur in tricuspid area, rate 130, regular. Blood pressure 120/60 mm. Lungs: rhonchi in front, slight dullness at bases, numerous fine

crepitations, respirations 34. Abdomen: liver and spleen enlarged, no ascites. Slight oedema of legs. Urine: S.G. 1018, trace of albumin, no casts or R.B.C. seen. Wassermann reaction negative. Blood culture positive - pure growth of streptococci from all tubes.

Died on 15.2.30. Diagnosis confirmed at autopsy, chief points of latter being as follows :-

Cardiac dilatation - left ventricle moderately hypertrophied, right ventricle enlarged transversely. Aortic valve showed presence of thick, gritty, fairly recent vegetations, encroaching on mitral orifice. Evidence of chronic endocarditis of mitral valve, which was stenosed and incompetent. Tricuspid orifice dilated. Liver enlarged and stenosed, venous congestion. Spleen enlarged and congested, two infarcts present. Kidneys slightly enlarged and congested, no visible infarcts. Cortices normal. Congestion and oedema at bases of lungs.

Case 53. Male, aged 64; photographer. Heart failure, myocardial degeneration, arterio-sclerosis, aortic regurgitation. No history of etiological factors. Complains of giddiness, impairment of memory, precordial pain, and shortness of breath on slight exertion for 12 months. Since January 1930 nocturnal attacks of dyspnoea, orthopnoea, cough, swelling of feet, and general exhaustion.

Admitted 10.2.30. Pale, orthopnoeic, dyspnoeic and slightly cyanosed, slight engorgement of cervical veins. Temperature 98° F.

Heart: apical impulse diffuse and feeble, left border $6\frac{1}{2}$" from mid-line in sixth space, systolic murmur at apex propagated to axilla; double aortic "to-and-fro" murmur present, extra-systoles and pulsus alternans, rate 120. Electrocardiogram shows right bundle branch block. Blood pressure 165/80 mm. Lungs: breath sounds impaired at bases, and fine moist râles present, respirations 30. Abdomen: liver enlarged, tender, no ascites. Oedema of legs. Urine: S.G. 1024, slight albumin, and an occasional hyaline cast. Wassermann reaction negative. Radial artery irregularly thickened.

Patient discharged himself against hospital advice on 19.2.30, still in serious condition. Subsequent history not known.

Case 54. Male, aged 40, clerk. Heart failure, infective endocarditis, rheumatic heart disease, mitral stenosis and regurgitation, aortic regurgitation. Rheumatic fever 1914, and "subacute rheumatism" in 1925. Scarlet fever at 12 years. Influenza in November 1929 and since then, complaining of increasing breathlessness, giddiness and faintness, bad cough, swelling of ankles and marked weakness and exhaustion.

Admitted 19.2.30; pale, orthopnoeic and dyspnoeic, cyanotic tinge of cheeks. Temperature 100.4° F. Heart: diffuse, feeble impulse, left border 6" from mid-line in seventh space, enlarged to right (deep cardiac dullness slightly over 1" to right of sternum), rough presystolic murmur at mitral area and loud mitral systolic murmur, audible at all other areas, and in axilla,

blowing aortic diastolic murmur conducted down sternum, rate 120, regular. Blood pressure 120/45 mm. Lungs: numerous fine crepitations at both bases, and slight impairment of percussion note, respirations 30. Abdomen: liver and spleen enlarged, some free fluid present. Oedema of feet and slight of legs. Urine: S.G. 1024, albumin present, red blood cells, a few hyaline casts. Wassermann reaction negative. Blood culture positive (streptococci present).

14.3.30. Died. Autopsy not granted.

Case 55. Male, aged 65; no occupation. Heart failure, arterio-sclerosis, aortic stenosis and regurgitation, chronic bronchitis and emphysema, auricular fibrillation. Giddiness, slight impairment of memory, headaches, dyspnoea on exertion, and occasional precordial pain, coming on for some years. Bronchitis each winter since 1922. For a few weeks before admission orthopnoea, oedema of legs, palpitations and dyspeptic symptoms.

Admitted 16.4.30: orthopnoea, marked dyspnoea and cyanosis, engorgement and pulsation of cervical veins, well-marked epigastric pulsation. Temperature 98° F. Heart: apex beat impalpable, and cardiac dullness obscured by emphysema, systolic thrill above right clavicle, aortic systolic murmur conducted upwards into neck, aortic diastolic murmur conducted down sternum, mitral systolic murmur propagated towards axilla, maximum in sixth space, 6" to left of mid-line, heart sounds faint, auricular

fibrillation, ventricular rate 140, radial pulse 110. Lungs: emphysema, rhonchi all over, scattered râles, numerous at bases, where percussion note impaired, respirations 32. Abdomen: liver enlarged, tender, ascites present. Oedema of legs and lumbar back. Urine: S.G. 1026, albumin present, a few hyaline casts. Radial artery irregularly thickened. Wassermann reaction negative

25.5.30. Improved. Dyspnoea and cyanosis slight. Slight oedema of legs only. Liver smaller, not tender. Lung bases much clearer. Faint trace of albumin in urine. Ventricular rate 80, no pulse deficit. Respirations 24.

29.5.30. Discharged at own request.

Case 56. Female, aged 14; schoolgirl. Heart failure, rheumatic heart disease, mitral stenosis, aortic regurgitation; ? adherent pericardium. Rheumatic fever at six years. Chorea at eight, and occasional attacks of tonsillitis, from the last of which, about 12 months before admission, patient dates her dyspnoea and palpitation on exertion. For a few weeks before admission, orthopnoea, swelling of legs and bad cough.

Admitted 18.6.30; malar flush, orthopnoeic, moderately dyspnoeic and fairly well-marked cyanosis, engorgement of veins in neck. Temperature 98° F. Heart: bulging and pulsation of precordial region, apex impulse diffuse and forcible, left border 5" from mid-line in sixth space, enlarged to right (deep cardiac dullness 1½" to right of sternum), systolic retraction in fourth and fifth spaces, systolic and faint diastolic murmurs at mitral

area, faint diastolic murmur down the sternum, rate 110, regular. Blood pressure 98/60 mm. Lungs: slight impairment of breath sounds at bases, and a few fine moist râles, respirations 28. Abdomen: liver enlarged, tender, no ascites. Oedema of legs. Urine: S.G. 1025, trace of albumin, no casts. Wassermann reaction negative.

16.7.30. Died. Autopsy not granted.

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