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The contracted plasma volume syndromes (relative polycythaemias) and their haemorheological significance

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> 'One of the remarkable qualities of the living organism's reaction to a variety of differing stressful exterior or interior factors is the generation of universal nonspecific responses.' (E. Matlina, 1984)

Of all the specialties in internal medicine, haematology is one which has had little difficulty differentiating disease from non-disease. Although at times, there may be difficulties placing a definitive diagnostic label on a disorder, haematologists have usually been able to define abnormality. The differentiation of reactive from malignant can, however, at times be difficult. Normality can be described in qualitative terms which are highly observer-dependent and based on experience (Isbister, 1986). Such would be the case in the interpretation of bone marrow samples and peripheral blood films. Secondly, normality may be defined in quantitative terms which are based on the use of reference ranges from a 'normal' population.

Neither qualitative, nor quantitative normality are absolute. This characteristic is only found when pathophysiology is the result of molecular abnormality in which circumstance a reference range is not required and the measurements are not observer dependent. The abnormal is differentiated from normal in clearly molecular terms where an abnormal protein is detected, or an abnormal amino acid or nucleotide sequence is identified as the cause of disease. Haematology has led the way in the identification of molecular diseases.

The polycythaemias provide us with a group of disorders where all types of normality may be encountered. At one end of the spectrum are polycythaemias due to an abnormal high-affinity haemoglobin molecule, which can be identified by biochemical or molecular biological techniques. At the other end are such ill-defined disorders as idiopathic erythrocytosis and relative polycythaemia, where differentiation of disease from non-disease is difficult, requiring statistical analysis with its inevitable problems of disease definition. Within this spectrum are other disorders, including secondary polycythaemia

due to hypoxia and myeloproliferative disorders for which qualitative analysis is required to clearly distinguish disease from non-disease.

In this review the relative polycythaemias, characterized by a contraction of the plasma volume whilst the red cell mass lies within the normal range, will be discussed. The relative polycythaemias have led to greater controversy between haematologists than most other haematological disorders. Some haematologists see no problem as they are 'non-believers' who state that any patient who has relative polycythaemia which is not explicable on the basis of an obvious clinical disorder (e.g. dehydration) does not have a definable disease—they do not accept that such a syndrome as stress polycythaemia exists. In contrast, there are haematologists, particularly those with a haemorheological interest, who are strong believers in the stress polycythaemia syndromes, and see them as a risk factor for the development of vascular disease. How is it that opposing views can exist within a specialty that traditionally has had few problems differentiating disease from non-disease?

HISTORICAL BACKGROUND

In the late nineteenth century it was first suggested that polycythaemia may have pathophysiological implications. In 1903 Sir William Osler described the association of polycythaemia and splenomegaly as a disease entity. It was only two years later that Gaisbock (1905) suggested that there was a second type of polycythaemia in which splenomegaly was absent, but hypertension and stress were important features. He introduced the term 'polycythaemia hypertonica'. Both Osler and Gaisbock indicated that some cases of polycythaemia may be related to haemoconcentration rather than a true elevation in the total number of circulating red cells (Osler, 1903; Gaisbock, 1905). Keith et al (1915) described patients with 'polycythaemia hypovolaemia' in whom they attributed the polycythaemia to a decrease in plasma volume. However, at that time accurate techniques were not available for the specific measurement of red cell mass or plasma volume and it was not until the late 1940s and early 1950s that detailed red cell mass and plasma volume measurements could be made using radio-isotopes or dye dilution methods. In 1940 Bassen and Abel introduced the concept of pseudopolycythaemia, where the peripheral blood polycythaemia was demonstrated by specific measurement to be due to diminished plasma volume. Although it had been emphasized by Gaisbock (1905) and other early workers that patients with this relative polycythaemia appeared to have an increased incidence of psychological stress, hypertension and obesity, it was not until Lawrence and Berlin (1952) described a series of 18 patients with relative polycythaemia that the concept of the polycythaemia of stress was introduced. These workers suggested that stress may cause plasma volume contraction in a similar manner to the stress of hypoxia, where it had been clearly demonstrated that the initial rise in haematocrit on ascent to high altitude was due to plasma volume contraction.

By the early 1960s the term stress polycythaemia was accepted, but its true

aetiology debated. Various terms, including stress polycythaemia, pseudo-polycythaemia, spurious polycythaemia, benign polycythaemia, Gaisbock's syndrome and 'red face with reduced plasma volume' were used to define this entity (Blum et al, 1959; Kuang and Peterson, 1962; Russell and Conley, 1964; Hall, 1965; Davies et al, 1974; Weinreb and Shih, 1975). This syndrome included patients who had chronic elevation in venous haematocrit due to plasma volume contraction and in whom dehydration and capillary leak had been excluded as a cause. The concept of psychological stress causing a relative polycythaemia has not been widely accepted. Although this group of patients appear to have a high incidence of stress it has been difficult to demonstrate that psychological stress induces a contraction in plasma volume.

During the last ten years there has been much scepticism and questioning of the concept of relative polycythaemia and stress polycythaemia. Brown et al (1971) have gone as far as describing stress polycythaemia as a non-existent disease. They conclude that these patients represent the statistical minority beyond two standard deviations of the confidence limits for haemoglobin. Fessel (1965) had previously taken a similar approach and referred to these patients as 'odd men out'. He went on to state that 'benign polycythaemia is neither a disease *sui generis* nor a syndrome demanding nosological recognition', and to support Wintrobe that there is probably no such entity.

There have been numerous studies in the last decade attempting to clarify the nature of stress polycythaemia, its haemorheological significance and approaches to therapy. To complicate the story even further it has only been during the last ten years that smoking, alcohol and hypoxia have been recognized as causes of plasma volume contraction and relative polycythaemia. Removal of these stimuli has in many cases resulted in resolution of the polycythaemia. There have also been studies indicating that adrenergic stimulation and stress may result in haematocrit elevation secondary to plasma volume contraction.

Unfortunately, in most studies workers have concentrated on the specific measurements of red cell mass and plasma volume, and have not taken into account the interactions between these parameters and circulatory control (Bentley and Lewis, 1976). This aspect has been emphasized more by those working on hypertension. Velasquez et al (1974) were the first to suggest that stress polycythaemia may be primarily a disorder of vascular volume control (i.e. compliance), thus emphasizing the relation between cardiovascular, blood volume and haematocrit controls. This concept has subsequently been developed by Isbister (1984, 1987).

There have been several studies emphasizing the morbidity and mortality associated with elevation of the haematocrit (Tohgi et al, 1966; Kannel et al, 1972; Cullen et al, 1981; Carter et al, 1983; Lowe et al, 1983; Pearce et al, 1983; Kiyohara et al, 1986; see also Chapter 9). Throughout this century it has been repeatedly suggested that hyperviscosity associated with polycythaemia may be responsible for arterial occlusive disease. Burge et al (1975) described a six times greater than expected death rate in following up 35 patients with relative polycythaemia.

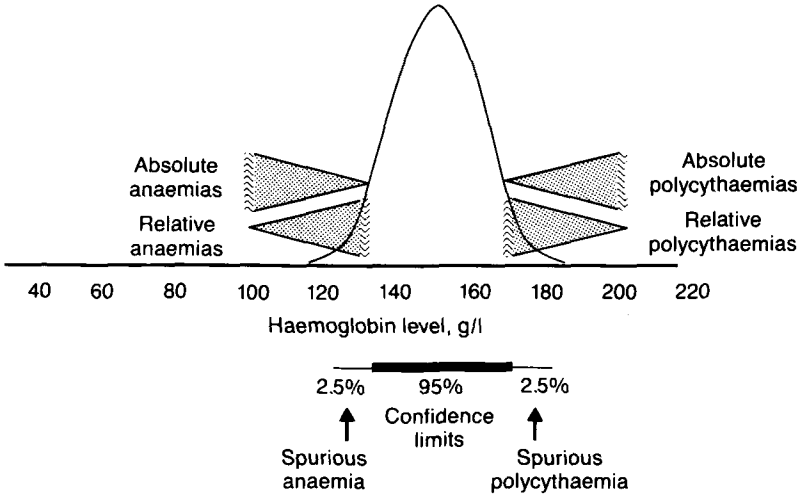

Figure 1. The reference range for venous haemoglobin, illustrating the relative and absolute polycythaemias and anaemias. Spurious anaemia and polycythaemia are represented by the 2.5% of normal people who lie outside the 95% confidence limits for haemoglobin.

TERMINOLOGY AND DEFINITIONS

The subject of relative polycythaemia has been plagued by problems of terminology. The terms used have frequently implied pathogenesis without justification. Definitions of the terms used in this paper are given below (see also Figure 1).

Relative polycythaemia

This is a broad term encompassing all polycythaemias secondary to plasma volume contraction in the presence of a normal red cell mass. The term in no way implies the mechanism(s) of the plasma volume contraction and is probably the best term to use when the aetiology has not been elucidated. The term haemoconcentration may be regarded as synonymous with relative polycythaemia. Relative polycythaemia may be acute or chronic, depending on the time course.

Stress polycythaemia

I prefer to define stress polycythaemia as acute or chronic relative polycythaemia on the basis of plasma volume contraction secondary to primary contraction of the vascular compartment. Stress polycythaemia is probably the term which has created the greatest confusion. It has generally been applied to chronic relative polycythaemia where dehydration has been excluded. In the absence of other aetiologies, psychological stress has been

accepted as the stress referred to in the definition. However, as will be pointed out, various physical stresses may cause acute or chronic plasma volume contraction (Isbister, 1984).

Spurious polycythaemia (statistical polycythaemia)

This term should be confined to the 2.5% of the normal population who lie above two standard deviations of the mean for the reference range of haemoglobin level. There are, however, two major stumbling-blocks to its use. Firstly, the problem of establishing a reference range and secondly, the differentiation of disease from non-disease. Diagnosis is by exclusion, as there are no definitive tests for the relative polycythaemias. Definition of the spurious polycythaemia group is thus difficult.

Obsolete and unsatisfactory terms

Several terms of historical interest should not be used. These include: polycythaemia hypertonica, Gaisbock's syndrome, pseudopolycythaemia, benign polycythaemia and apparent polycythaemia.

NORMAL CONTROL OF VENOUS HAEMOGLOBIN/ HAEMATOCRIT

Although venous blood haemoglobin and haematocrit are the simplest and most frequently measured laboratory parameters, there is increasing debate as to their normal reference ranges in a healthy population and also their levels in various physiological adaptations (e.g. high altitude, pregnancy, exercise) and disease states (e.g. respiratory, cardiac and vascular disease). The definition of a normal population is difficult when smoking, stress, temperature and physical fitness may all influence the result. It is generally felt that the currently accepted upper limits for haemoglobin level of 180 g/l in males and 165 g/l in females are probably inappropriately high.

The red cells are the major contributors to the viscosity of blood. Firstly, the total number of red cells, as reflected in the haemoglobin level is important and secondly, the fluidity of individual red cells and their aggregation potential further contribute to the whole blood viscosity level at various haemoglobin levels. Up to approximately a haemoglobin of 100 g/l or haematocrit of 0.30, blood behaves as a Newtonian fluid in that viscosity is not shear rate dependent. In contrast, above these levels, the viscosity enters an exponential phase in relation to haemoglobin level, and at the same time progressively behaves as a non-Newtonian fluid. This non-Newtonian characteristic by which blood becomes more fluid at higher shear rates, known as thixotropy, is due to the remarkable flexibility of the anuclear red cell.

Another important concept is the physiological haemodilution of blood which occurs in the normal microcirculation. The measured venous haemoglobin does not represent the dynamic physiological level in organ capillaries where gas exchange is occurring. The measured venous haemoglobin is not a

true representation of the functional level in the individual organ microcirculations. The individual organs of the body are able to autoregulate their microcirculatory flow and haemoglobin level by vasomotion.

The 'set point' for haemoglobin/haematocrit

The normal 'set point' for the venous haemoglobin is determined by several factors, but surprisingly little is known about the sensor mechanisms involved in its determination. Although much is understood about blood volume, plasma volume and red cell mass control, surprisingly little is known about what determines the ratio between the red cell mass and plasma volume and, in effect, the peripheral blood haemoglobin or haematocrit level and thus viscosity.

On reviewing the literature, one would be excused for incorrectly thinking that red cell mass and plasma volume are independent variables. There is quite good understanding of the sensors and effectors which control circulating blood volume, the size of the vascular compartment, perfusion pressure, cardiac filling pressure–volume relationships, plasma volume and the red cell mass. The neuroendocrine system, via the autonomic nervous system, renin–angiotensin system, vasopressin and atrial natriuretic factor clearly have important roles in determining vascular tone as reflected in total peripheral resistance and venous compliance (Greenway, 1983; Rothe, 1983; Robertson, 1983; Needleman and Greenwald, 1986). In particular, the size of the venous capacitance compartment and its compliance are controlled by these neuroendocrine mechanisms. Individual organ capillary filtration is highly dependent on the intracapillary pressure as determined by the arteriolar tone and venous pressure. The renal handling of salt and water, via vasopressin, renin–aldosterone and atrial natriuretic factor, play key roles in controlling the circulating plasma and interstitial volumes. Cardiac filling pressures, and as a consequence cardiac output, are ensured by the maintenance of a correct relationship between the size of the vascular compartment and the volume of fluid in the circulation.

Red cell mass, plasma volume and viscosity control

The red cell mass is controlled via erythropoietin, secreted by the kidney. Tissue hypoxia is the stimulus for erythropoietin production, with sensors presumably placed in the renal circulation. As the kidney receives a blood supply in gross excess of its oxygen requirements, oxygen extraction from haemoglobin as reflected in the arterio–venous oxygen difference is small compared with most other organ circulations. This means that haemoglobin circulating through the kidney is working in the high-saturation plateau of the oxygen-association curve. These circumstances make the kidney an ideal organ in which to place the sensor mechanism to detect minor changes in haemoglobin/oxygen saturation. If such a sensor was placed in an organ working on high oxygen extraction (e.g. in the coronary circulation) an insensitive regulation system would result and 'fine tuning' of red cell mass would not be possible.

Thus the kidney, under the higher influence of the autonomic nervous system, is placed in a key position to control the circulation and oxygen transport. However, the relationship between the red cell mass and plasma volume has still not been explained. Dintenfass (1976) has postulated a viscoreceptor for sensing blood viscosity and controlling haematocrit. Although evidence for this viscoreceptor is lacking, logic would support the concept of a sensing mechanism registering blood fluidity and, presumably via the effector mechanisms discussed above, regulating the relationship between plasma volume and red cell mass. Some animals, such as the horse, have a large reserve of red cells which can be injected into the circulating blood volume from the spleen when needed. However, humans have little reserve of non-circulating red cells and are unable to acutely change the circulating red cell mass. Any acute changes in the haematocrit, and thus oxygen carrying capacity of blood, must occur as a result of changes in plasma volume.

If this postulated viscoreceptor does exist, logic again would suggest location in the renal vessels. The renal circulation is a high flow system with large capillaries (diameter 10 μm) which are less sensitive to viscosity changes than those in other organ microcirculations. For the same reasons given for the detection of tissue hypoxia, the renal circulation would be in an ideal location to detect changes in blood viscosity before they become of major significance to other circulations in the body. Appropriate compensatory changes in plasma volume and/or red cell mass could be made.

The optimal haemoglobin/haematocrit

Haemoglobin and haematocrit can be measured with a high degree of accuracy and reproducibility. Although there may be diurnal variations in the levels (up to 5%), ranges greater than this need explanation and cannot be attributed, as they commonly are, to laboratory error. Although the venous haematocrit only represents the ratio of the cellular components of blood to plasma and tells us little, if anything, about total volume and distribution of these components within the body, there is a tendency to over-interpret the information provided by a single haematocrit or haemoglobin measurement. If serial changes occur and clinical information is known about the patient, it is frequently possible to deduce what changes may have occurred in the red cell mass and plasma volume.

The reference range for haemoglobin is relatively wide and, as mentioned, there is difficulty in defining a normal population. Now that it is known that different reference ranges are found when fitness, smoking, alcohol and stress are taken into account it becomes more difficult to establish a true reference range. If physically fit, non-stressed, non-smoking and non-drinking people were selected for the reference range then probably less than 10% of supposedly healthy people would be eligible for establishing reference ranges for haemoglobin and haematocrit.

From these considerations it is apparent that the question of the 'optimal haematocrit' is complex. Cardiac filling pressures and volumes, tissue hypoxia, acid/base disturbances and probably viscosity, all play a role in determining the relationship between the red cell mass and plasma volume.

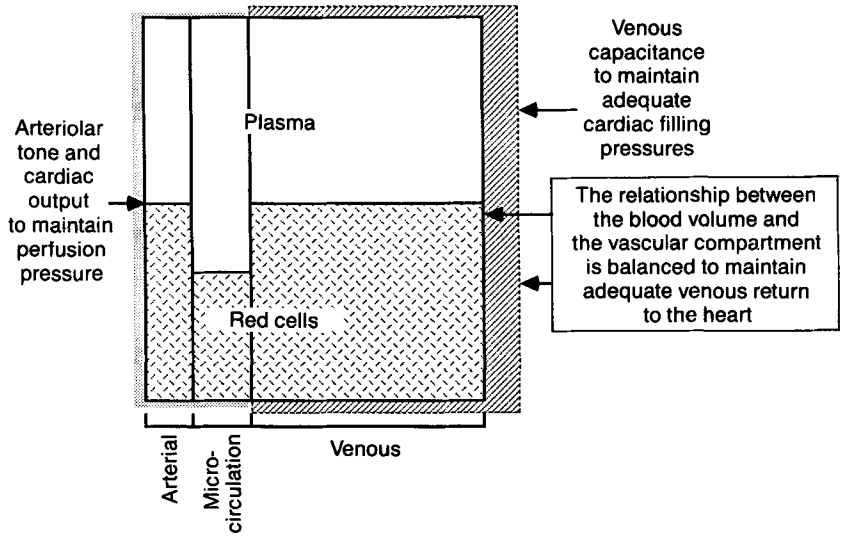

Figure 2. The relationship between the blood volume (red cell mass plus plasma volume) and the volume of the vascular compartment. The lower haemoglobin level in the microcirculation represents normal haemodilution (see text). ▨ = Arterial constrictor reserve; ▨ = Venoconstrictor reserve.

Under appropriate stresses, whether they be hypoxia, increased oxygen demand or volume loss, the oxygen transport system will be able to compensate and maintain the various parameters discussed above at appropriate levels. As with all adaptations, the system has limits and with multiple stresses, or in various disease states, the adaptations occurring may not ultimately be in the best interest of the organism. However, in the short term, they may be appropriate and life saving as long as other insults are not superimposed.

The role of circulatory regulation and venous compliance in haematocrit changes

The central role of venous capacitance in maintaining cardiac filling pressures and volumes is well known. However, it is only in recent years that greater attention has been directed towards the control mechanisms of the venous system (Rothe, 1983, 1986; Harrison, 1985). Most attention has centred on the arterial and cardiac aspects of circulatory control. However, it was pointed out long ago by Starling that venous pressure is important in the transcapillary forces. Many physiologists have also emphasized that the heart can only pump out as much blood as it receives and thus control mechanisms on the venous side of the heart for regulating cardiac filling volume and pressure must have equal importance along with arterial circulatory control.

The role of venous compliance in determining cardiac filling pressures and volumes and its relation to haematocrit is important (Figure 2). As most of the

hormones involved in blood volume and pressure control are capable of altering the ratio between the red cell mass and plasma volume, it is important that these sensor and effector mechanisms in cardiovascular control are considered in relation to the determination of venous haematocrit (Sjostrand, 1976).

If there is an acute change in the relationship between the size of the vascular compartment and the blood volume, any corrections to re-establish appropriate cardiac filling pressures must be made by changes in venous capacitance or plasma volume. There are thus important relationships between venous compliance and plasma volume. In chronic adaptation, changes in red cell mass may also be involved. If there is acute volume loss from the circulation, cardiac filling is initially maintained by increasing venous tone and centralizing the capacitance venous blood, especially splanchnic (Greenway, 1983; Rowell and Johnson, 1984). This is an acute mechanism, and during the ensuing minutes and hours, there is a transcapillary refilling and activation of salt- and water-retaining hormones, resulting in haemodilution. On the contrary, if venous compliance is suddenly increased without blood volume change, relative hypovolaemia will occur, cardiac output will fall and the situation will not be corrected until salt- and water-retaining hormones and transcapillary refilling increase the plasma volume to restore cardiac filling pressures, again with haemodilution.

When venous compliance is reduced (by venoconstriction) in the presence of a fixed blood volume a redistribution of the blood volume will occur. Barnes et al (1986) have shown in cats that stimulation of the splanchnic sympathetic nerves causes an increase in aortic pressure and right atrial pressure. The pattern resembles that resulting from the infusion of whole blood. The centralization of blood from the venous capacitance compartment will lead to overfilling of the heart and atrial distension. Unless the cardiac output increases, the cardiac filling pressure will remain inappropriate. The atrial volume receptors will be activated, leading to the release of atrial natriuretic factor. Unless the venoconstriction is relieved, the only way of re-establishing the correct relationship between the size of the vascular compartment and the blood volume is to reduce plasma volume. This plasma volume contraction is achieved by salt and water shift into the interstitial space and/or a diuresis. A most interesting study by Fluckiger et al (1986) demonstrated that atrial natriuretic factor can elevate the haematocrit level in the nephrectomized rat, suggesting that this hormone has direct effects in facilitating fluid movement from the plasma into the interstitial compartment. A plasma volume contraction of 10% was observed.

There are various mechanisms by which venous compliance may be reduced, the most important being via the sympathetic nervous system. Stimuli that may activate these pathways include hypoxia, exercise, cold exposure and mental stress. Sympathetic activation or the infusion of α-receptor agonists, such as noradrenaline, which cause venoconstriction, lead to a reduction in the total circulating blood volume as a result of plasma volume contraction, haemoconcentration and blood hyperviscosity (Finnerty et al, 1958; Cohn, 1966; Hainsworth et al, 1983; Bennett et al, 1984; Matlina, 1984; Ehrly, 1985; Appleton et al, 1986). Cohn (1966) demonstrated that the

greatest plasma volume contraction occurred with adrenaline and ephedrine, which produce arteriolar vasodilatation in association with venoconstriction. Weil and Chidsey (1968) confirmed the important role of the sympathomimetic system in blood volume and haematocrit control by inducing adrenergic blockade with guanethidine and phenoxybenzamine. In each case plasma volume increased and haematocrit fell. In ten subjects given guanethidine, plasma volume increased from a mean of 2480 ml to 3440 ml (i.e. 21% increase), with haematocrit falling from 0.467 to 0.443. Isosorbide dinitrate (a venodilator) has a similar effect with haemodilution and a fall in blood viscosity (Hossmann et al, 1981).

The effects of stresses on the blood volume and haemoglobin/haematocrit control

There are various normal and abnormal stresses on the circulation oxygen transport in which there may be a contraction of the plasma volume secondary to reduction of the total blood volume. The circulation responds as if it were hypervolaemic, i.e. the container has reduced in size, but the contents have remained constant. The mechanisms outlined above are thus activated to re-establish pressure–volume relationships in the circulation. The resulting elevation in haematocrit is 'unavoidable' and its rheological significance will depend on the presence or absence of other defects and/or stresses on the circulation. On the other hand, there may be teleological advantages in acute elevation of the haematocrit, such as increased oxygen carrying capacity in hypoxia.

DIAGNOSIS OF RELATIVE POLYCYTHAEMIA

The hallmark differentiating absolute polycythaemia and relative polycythaemia is red cell mass and plasma volume measurement (Figure 3) (Pearson and Guthrie, 1984; Pearson et al, 1984). There are, however, several clues which may establish with high probability the group in which a patient lies.

1. There may be associated clinical or laboratory features clearly supporting a diagnosis of myeloproliferative disease. In other cases there may be clearly identifiable stimuli to absolute polycythaemia, such as severe long-standing hypoxic lung disease, cyanotic heart disease or a family history of a haemoglobin abnormality.
2. If the haemoglobin level is less than 200 g/l and shows significant fluctuation from day to day, particularly following admission to hospital, relative polycythaemia is the likely diagnosis.
3. Clinical features of hypervolaemia and/or hyperviscosity are suggestive of absolute polycythaemias, particularly polycythaemia rubra vera.

In many patients with only mild polycythaemia, red cell mass and plasma volume measurements may not be necessary. In many patients the clinical features and the haematocrit changes following admission to hospital allow one to infer the diagnosis of relative polycythaemia. If the haemoglobin level is

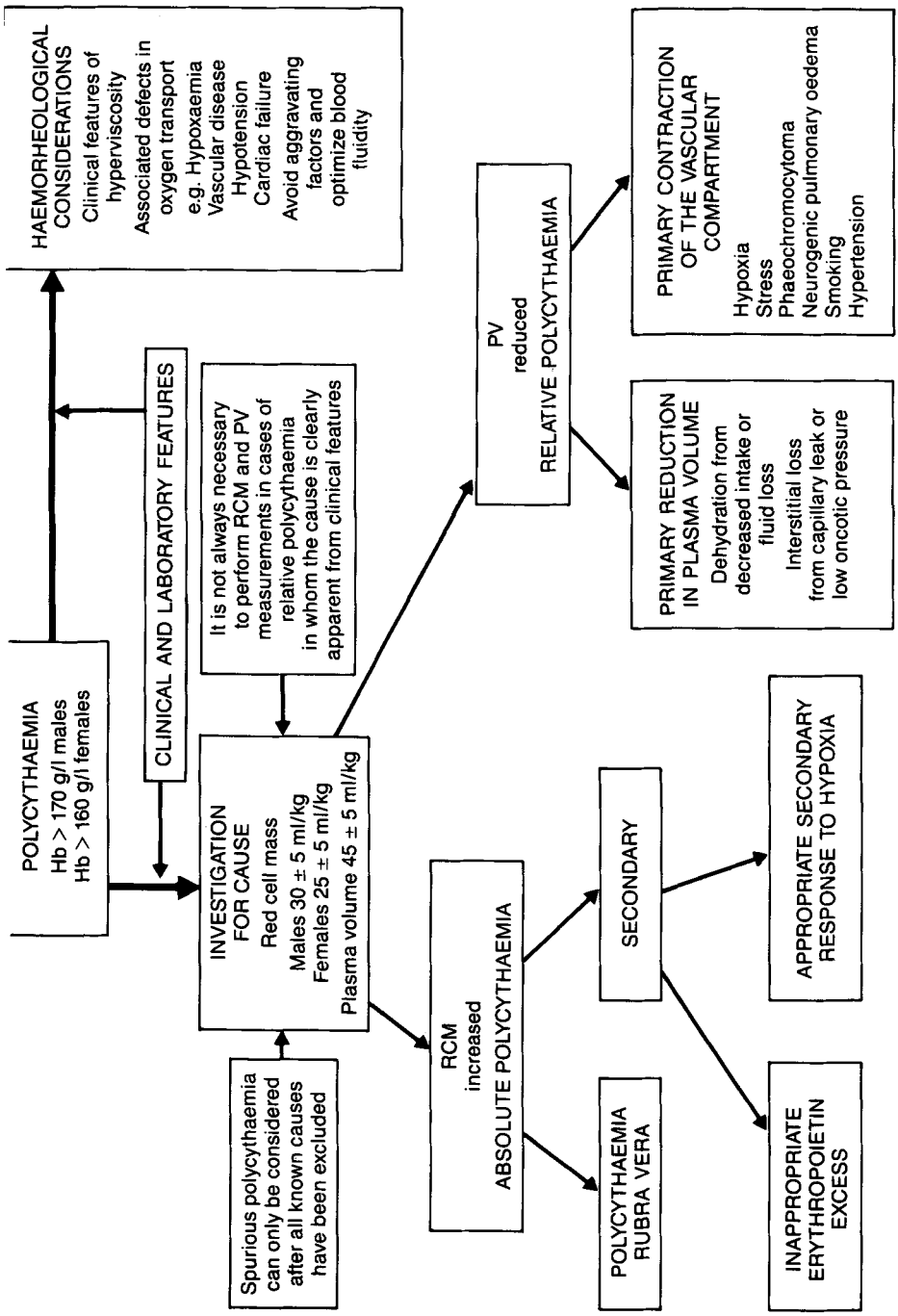

Figure 3. An algorithmic approach to the investigation of polycythaemia, with an emphasis on the relative polycythaemias.

Table 1. Classification of relative polycythaemia*.

Primary contraction of the plasma volume
Dehydration
Decreased intake; hypodipsia
Fluid loss: gut, diuresis, skin, salt-water drowning
Capillary leak syndromes
Anaphylaxis, cold urticaria, septicaemia, basophil/mast cell disorders, burns
Pre-eclamptic toxaemia(?)
Envenomation
Reduced oncotic pressure
Nephrotic syndrome, liver disease, protein-losing gastroenteropathy
Third spacing:
Trauma, acute local oedema, acute ascites, effusions
Primary contraction of the vascular compartment
Hypoxia
Arterial hypoxia, carbon monoxide, cyanide
Cigarette smoking
Idiopathic stress polycythaemia
Chronic
Acute: e.g. myocardial infarction, stroke, acute psychological stress
Pre-eclamptic toxaemia (could also be capillary leak)
Essential hypertension
Neurological disorders
Stroke, head injury, Guillain–Barré syndrome
Phaeochromocytoma

* The group of people with spurious polycythaemia who represent the 2.5% of normal individuals with haemoglobin values above the 95% confidence limits are difficult to identify and this should usually be done by exclusion.

above 200 g/l, most patients are likely to have absolute polycythaemia (Figure 1). In contrast, below this level relative polycythaemia is more common. As red cell mass and plasma volume measurements are not always rapidly and readily available, a presumptive diagnosis of relative polycythaemia is frequently made and therapy proceeds on that assumption. In the less urgent circumstance where a patient is referred for the investigation of chronic polycythaemia, time permits definitive study of red cell mass and plasma volume. It is in this group that the more controversial question of the aetiology of relative polycythaemia arises. Figure 3 summarizes the decision tree for polycythaemia, especially relative polycythaemia.

CAUSES OF PLASMA VOLUME CONTRACTION (RELATIVE POLYCYTHAEMIA)

The contracted plasma volume syndromes can be broadly divided into two groups (Table 1). There is, however, the difficult group of people with spurious (or statistical) polycythaemia who represent the 2.5% of normals who are

above the 95% confidence limits for the haemoglobin level. These people can only be identified by exclusion of all known causes of relative polycythaemia. The first group of patients with relative polycythaemia are those in which there is a primary reduction in the plasma volume with a secondary compensation from the cardiovascular system to maintain the circulation (Isbister, 1984). In this group are included severe dehydration from salt and/or water loss, capillary leak syndromes, hypo-oncotic pressure, third spacing and chronic hypodipsia. Most of these are acute disorders and the diagnosis is supported by other clinical and laboratory features. The second group of relative polycythaemias are those in whom the primary disorder is a contraction of the vascular compartment. This is the group that I elect to call the stress polycythaemias. The contraction of plasma volume in this group is a secondary compensation to avoid central hypervolaemia, and in the case of hypoxia, to increase oxygen carrying capacity.

This differentiation between the two types of plasma volume contraction is important, particularly for management. Unless this differentiation is made, the confusion and controversy as to the nature and aetiology of the relative polycythaemias will continue. As will be pointed out, there are many stimuli which may be responsible for acute or chronic stress polycythaemia. The term stress is used in its broadest sense, as originally suggested by Lawrence and Berlin (1952) in their landmark paper on the nature of polycythaemia and relative polycythaemia. As with most of the polycythaemias, both absolute and relative, there is rarely a single definitive test which allows categoric diagnosis. In most patients assessment of the clinical and laboratory features is required for diagnosis.

RELATIVE POLYCYTHAEMIA DUE TO A PRIMARY CONTRACTION OF THE PLASMA VOLUME

Dehydration

Acute or chronic dehydration may be the cause of plasma volume contraction and thus relative polycythaemia. However, polycythaemia from dehydration alone requires a marked reduction in total body water. Water is distributed between the plasma volume, interstitial and intracellular compartments in the ratio of approximately 1 to 4 to 5 respectively. The vascular compartment also has priority over the interstitial compartment in order to maintain the circulation. Thus, if a patient has significant polycythaemia secondary to dehydration alone this is usually apparent from the clinical history and physical findings and the cause is usually simple to establish. Broadly, the causes are divided into those of decreased intake, increased loss, or a combination of both. The group which has received most attention in recent years is that where dehydration results from chronic hypodypsia. This may be seen in the elderly or in relation to neurological disease (Seymour et al, 1980; Miller et al, 1982; Robertson, 1983). The pathophysiology of this group involves a disturbance of the osmoregulation and thirst centres. Keatinge et al

(1986) have recently correlated elevations in haematocrit and blood pressure with heat stress, and suggested that dehydration may be responsible for the increased incidence of myocardial infarction and stroke during heat waves.

Capillary leak syndromes

Any condition which causes a generalized capillary leak with plasma volume loss is likely to result in hypovolaemia and haemoconcentration. Capillary leak may be seen in association with a variety of infectious, inflammatory, allergic and toxic disorders. Of particular interest is hereditary angioneurotic oedema in which there may be haemoconcentration during an attack. The same may be seen in the cold urticaria syndrome and in various basophil and mast cell disorders which may cause a marked release of histamine. Burns constitute another important condition resulting in capillary leak.

Hypo-oncotic relative polycythaemia

Severe hypoproteinaemia, as seen in conditions such as nephrotic syndrome, liver disease or protein-losing gastroenteropathy may cause relative polycythaemia.

Third spacing of fluid

Trauma, acute local oedema formation and acute ascites may lead to loss in plasma volume and haemoconcentration.

POLYCYTHAEMIA SECONDARY TO CONTRACTION OF THE VASCULAR COMPARTMENT (REDUCED VENOUS COMPLIANCE): THE STRESS POLYCYTHAEMIA SYNDROMES

In this group of polycythaemias the primary mechanism of reduction in plasma volume is a secondary compensation, resulting from constriction of the venous capacitance vessels. A patient who normally has a haematocrit towards the upper limit of the normal range becomes polycythaemic as a result of the secondary plasma volume contraction. These changes may occur as an appropriate response to an identifiable stimulus, or there may be inappropriate autonomic nervous system activation. The sympatho-adrenal system plays an important role in homeostasis in the face of widely varying external environments. The activation of the sympatho-adrenal system acts to preserve homeostasis by increasing cardiac output and modifying blood volume distribution, usually with the aim of ensuring oxygen delivery to the tissues. Table 1 summarizes the various contracted plasma volume syndromes in which the primary response or disorder is an alteration in cardiovascular pressure–volume relationships.

Hypoxia

It was Lawrence and Berlin (1952) who first pointed out that the classic form of stress polycythaemia in which plasma volume was contracted could be seen in acute hypoxic stress of altitude. Considerable work has been done since, confirming that the initial response to acute hypoxia is an increase in sympatho-adrenal activity, manifest as increased cardiac output, venoconstriction, centralization of the blood volume and subsequent haemoconcentration (Chalmers et al, 1965; Cunningham et al, 1965; Korner and White, 1966; Weil et al, 1969; Cruz et al, 1976; Hannon and Vogel 1977; West, 1982; Richalet et al, 1983; Escourrou et al, 1984; Favier et al, 1985; Mathew et al, 1985; Rothe et al, 1985). Hainsworth et al (1983) have demonstrated in dogs that hypoxic stimulation of the aortic and carotid chemoreceptors results in decreased splanchnic venous capacitance. Jaeger et al (1979) have confirmed that there is an acute increase in intrathoracic fluid volume on ascent to high altitude. Surks et al (1966) measured body fluid composition in five young males before and during ascent to 4230 metres (14 100 feet) on Pikes peak, Colorado. Although weight loss occurred, this was due to fat loss and total body water remained stable. However, there was a highly significant decrease in plasma volume after four and eight days, due to redistribution of plasma water. The net effect of plasma volume contraction is to increase oxygen capacity of the blood, albeit by reducing the total blood volume. This is only a short-term response as the circulation is placed in a precarious position and will have difficulty responding to further stresses or volume loss. Thus the long-term response to hypoxic stress is an increase in red cell mass and return of the blood volume towards normal.

The sleep apnoea syndromes may also be important in this respect as abnormal sleep patterns have been reported in stress polycythaemia (El-Yousef, 1972; personal observations). There are no studies in humans recording haematocrit or blood viscosity changes during sleep and sleep apnoea. Castellini et al (1986) carried out an interesting study in elephant seal pups, which showed a marked rise in haematocrit during episodes of sleep apnoea. It is now clear that some patients with chronic tissue hypoxia (as may be seen in chronic lung disease and chronic smoking) do not necessarily have an increased red cell mass. However, in many circumstances polycythaemia is due to plasma volume contraction, with little increase in red cell mass. The reason why some patients respond in this way and others increase their red cell mass remains unclear, but it may be time related, due to the intermittent nature of the hypoxic stress, variable responses of the adrenergic system or related to the arterial P_{CO_2} concentration. Down-regulation of the α-adrenergic receptors during chronic hypoxia in spontaneously hypertensive rats has been demonstrated, supporting the concept of variable sympathetic responsiveness (Henley and Tucker, 1986). The arterial carbon dioxide tension may also be an important determinant of the neuroendocrine response to hypoxia. Rothe et al (1985) have demonstrated in dogs that severe systemic hypercapnia is a greater stimulus to reduced venous capacitance than hypoxia alone. Interestingly, hypocapnia has also been shown to accentuate the venoconstriction response to hypoxia (Eckstein and Horsley, 1960).

Carbon monoxide

Impaired tissue oxygenation by mechanisms other than arterial hypoxia will also result in adaptive changes in oxygen transport. For example, carbon monoxide may be responsible for inactivation of a component of circulating haemoglobin as well as increasing affinity of the remaining functional haemoglobin. The adaptive responses to this may be similar to the above, but it is also possible that increased capillary permeability may play a part (Siggaard-Anderson et al, 1968; Ramsay, 1969; Astrup, 1972; Stonesifer, 1978). In the short term there is contraction of plasma volume whereas in some patients, with longer-term exposure, there may also be increase in the red cell mass.

Cigarette smoking

Smokers, as a group, have a higher mean haematocrit level than non-smokers (Eisen and Hammond, 1956; Isager and Hagerup, 1971). It has been observed that acute changes in smoking habits will result in fluctuations in the haemoglobin level (Markman, 1981; personal observations). Smoker's polycythaemia probably has an overlap with the effects of carbon monoxide exposure and the idiopathic stress polycythaemia syndrome discussed below. Red cell mass and plasma volume measurements in smokers with polycythaemia demonstrate that some patients have both parameters within the normal range, but red cell mass towards the upper limit of normal and the plasma volume at the lower limit of normal (Sagone and Balcerzak, 1975; Smith and Landaw, 1978). In others there is a clear elevation in the red cell mass or a reduction in the plasma volume. There has been debate as to the mechanism of plasma volume contraction, but it would appear that a combination of contraction of the vascular compartment secondary to hypoxia, direct stimulatory effects on the sympathetic nervous system (Cryer et al, 1976; Baer and Radichevich, 1985) and possible capillary leak are responsible.

Idiopathic stress polycythaemia

I prefer to use the term idiopathic stress polycythaemia to describe those patients who appear to have a stress polycythaemia from the mechanisms described above, and in whom the 'stressor(s)' are difficult or impossible to identify. Further subdivision of this group will probably continue in future years as the underlying stimuli are identified. In many cases psychological stress may be an important factor, however this has been difficult to prove in patient population studies (Benitone and Kling, 1970; Schuber and Rohira, 1981; Mathew and Wilson, 1986). However, it may be that certain people are particularly susceptible to this syndrome and this subgroup is difficult to identify in population studies. Specific behaviour patterns have been identified with hyperactivity and hypersensitivity of the adrenergic system (Editorial, 1982; Eliasson, 1984; De Quattro and Hamad, 1985). Stress has always been difficult, if not impossible, to define. Most workers in the area would now agree that stress in not defined by the stimulating event nor the direct effect on

the subject, but rather the individual's reaction to what happens. Connections between central nervous system function and central and peripheral cardiovascular control are well accepted, as are connections of a neuroendocrine nature. There are thus logical mechanisms by which stress may interact with blood volume. Ehrly et al (1986) has recently confirmed that acute psychological stress may lead to an elevation in haematocrit and hyperviscosity. Extreme stress in humans is associated with acute adrenergic activation and cardiac lesions (Cebelin and Hirsch, 1980). As these are postmortem investigations it has not been possible to comment on blood volume and haematocrit which were not measured.

Obesity, diabetes, alcohol (Smith and Lucie, 1973; O'Brien et al, 1981; Howes and Reid, 1986) and hypertension (Emery et al, 1974) are common factors for patients with this syndrome, but their roles remain unclear. The sympathomimetic response to various stresses, including psychological stress has been well studied (Ward et al, 1983). Blizzard and Morris (1986) have demonstrated that acute stress in rats induces a sharp increase in plasma concentrations of atrial natriuretic factor, which will result in haemoconcentration. Whether this rise is a direct effect of stress or a secondary response to sympathomimetic activity remains to be clarified.

Idiopathic stress polycythaemia will no doubt include people with spurious polycythaemia, and identification of these patients is difficult. It should not be concluded that all patients in whom the cause of a relative polycythaemia cannot be identified have spurious polycythaemia. It has been my experience that some patients, who have had a normal haemoglobin in the past, present some years later with relative polycythaemia. It is also likely that those patients who truly represent the 2.5% above two standard deviations of the mean may be at risk of the haemorheological consequences of an elevated haematocrit.

With a more dynamic approach to the question of stress polycythaemia and the identification of aetiological factors, it has now been recognized that the various parameters (including haematocrit) in the haematological stress syndrome may fluctuate with time and in relation to various exogenous and endogenous stimuli. Although there is a need for large series of patients to be studied over time, clinical experience indicates that stress polycythaemia, other features of the haematological stress syndrome and its rheological consequences can be reversed if various aetiological factors can be identified and removed (Isbister, personal observation).

With all these common associations it is natural that there will be difficulties in elucidating causal relationships, and most of these factors are already known to be risk factors for vascular occlusive disease. Until a statistically significant association between all these variables is established it is difficult to analyse pathophysiological mechanisms. Several theories have been proposed relating polycythaemia to stress and the most tenable at present is the increased venous tone theory outlined above (Velasquez et al, 1974; Isbister, 1984, 1987). It is likely that many cases are multifactorial, with several risk factors interacting and compounding to induce the syndrome. In some cases, where hypertension is a feature, specific therapy for the hypertension is associated with a return of the haematocrit towards normal.

In patients where stimuli cannot be identified, particularly in elderly patients, dysfunction in blood volume control mechanisms at a central or peripheral level is an attractive hypothesis. Central autonomic abnormalities, deficiencies or excesses of volume and pressure hormones, and altered sensitivity of peripheral receptors are all possible mechanisms.

Pre-eclamptic toxaemia

Plasma volume contraction is a feature of pre-eclamptic toxaemia of pregnancy, and plasma volume expansion therapy may be beneficial (Gallery et al, 1981). The exact pathophysiology remains unclear, but haemodilution has beneficial effects on microcirculatory perfusion, where the main pathology appears to be centred.

Hypertension

The relationship of blood and plasma volume changes to blood pressure is a complex issue. Reports in the literature have been conflicting, but current evidence favours a reduction in plasma volume and elevation in haematocrit in association with essential hypertension (Bing and Smith, 1981; Kobrin et al, 1984) and noradrenaline-induced hypertension (Finnerty et al, 1958). Whether there is a proportional reduction in the red cell mass in some patients with the haematocrit unchanged is not known. There are several studies which indicate that patients with essential hypertension have exaggerated sympathomimetic responses to stimuli such as exercise, cold, hypoglycaemia, hypoxia, pain and psychological stress (Herd, 1984). It is unfortunate that haemorheological and haematological parameters are not reported in these studies. The significance of these findings in the aetiology and pathogenesis of hypertension is unclear. However, there is increasing interest in the role of venous capacitance vessels. The finding that venous compliance is reduced in essential hypertension and the spontaneous hypertensive rat model is important (London et al, 1978; Lundin et al, 1981; Ohlsson, 1982; Ohlsson et al, 1982; Tarazi, 1983, Burke et al, 1984). Therapy to control hypertension is commonly followed by a fall in haematocrit and blood viscosity when drugs such as prazosin which have a venodilatory effect are used (Letcher et al, 1979). The well known 'first dose effect' seen in some patients is due to the venodilating effect, followed by transcapillary refill and haemodilution (Isbister, personal observation).

Neurological disease

It is well accepted that hyperviscosity syndromes may have neurological manifestations, but the converse is not as well recognized. In many neurological disorders there may be massive inappropriate activation of the sympathetic nervous system with sudden outpouring of catecholamines (McLeod et al, 1982; Stein et al, 1983; Hachinski et al, 1986). The most florid example is seen in neurogenic pulmonary oedema, in which centralization of

the blood volume occurs in the presence of associated pulmonary venoconstriction (Lagerkranser et al, 1982; Malik, 1985). Acute pulmonary hypertension ensues with rupture of pulmonary capillaries and resultant pulmonary oedema. The acute loss of plasma leads to haemoconcentration and polycythaemia. The elevation of haematocrit, and occasionally, polycythaemia seen in some patients with acute stroke syndromes may have a similar mechanism, but whatever the cause the haemorheological consequences for the patient with stroke will be similar and haemodilution is usually appropriate therapy. Polycythaemia due to plasma volume contraction has also been reported in the Guillain–Barré syndrome, in which autonomic dysfunction occurs (Richards et al, 1985). This reversible haemoconcentration is generally inappropriately attributed to dehydration with scanty supportive clinical evidence.

HAEMORHEOLOGICAL SIGNIFICANCE OF PLASMA VOLUME CONTRACTION

With increasing recognition of the importance of blood fluidity (especially haematocrit) in relation to vascular disease, the stress polycythaemias and the haematological stress syndrome are no longer of purely theoretical interest. With arterial and venous occlusive diseases being of such major medical importance, haemorheology is establishing its rightful place alongside perfusion pressure and the vessel diameter in the triad of determinants of blood flow and tissue perfusion (Humphrey et al, 1979; Hudack et al, 1986).

The exponential rise in blood viscosity which is seen as the peripheral blood haematocrit rises above 0.45 has already been emphasized. The ultimate rheological significance of this higher blood viscosity is not solely determined by the haematocrit level, nor the measurable whole-blood hyperviscosity. Red cell deformability, qualitative and quantitative alterations in platelets, neutrophils and plasma proteins all interact with the haematocrit level to ultimately determine blood fluidity and organ perfusion (Chapter 1; Stuart 1984). Activation of the sympathetic nervous system, as well as being an important mediator of the plasma volume contraction, has other effects, including activation or elevation of platelets, neutrophils and various coagulation factors (Stuart, 1984). There are also the well-studied actions on the heart and circulation, metabolism and electrolyte balance (especially hypokalaemia: Reid et al, 1986).

Parallel to these blood fluidity changes, other defects in, or stresses on, the oxygen transport chain must be considered. The associated presence of arterial hypoxia, cardiac decompensation, large or small vessel disease and hypotension may all be important when fluidity of blood is threatened. It is thus not possible to take a unifactorial approach to the investigation and management of the acute and chronic stress polycythaemia syndromes. In chronic stress-induced polycythaemia, such as may be seen in the classic stress polycythaemia, or in chronic hypoxic lung disease, time permits a rational and unhurried assessment of the patient's management. In contrast, for acutely induced stress polycythaemia (as may be seen in acute hypoxia, acute

neurological disease, myocardial infarction, stroke or acute psychological stress) rapid therapeutic intervention may be necessary to correct a haemorheological crisis and thus avoid the precipitation of a vascular catastrophe or limit the extent of tissue damage of an established vascular occlusion. Sympathetic activation seen in acute myocardial infarction (Karlsberg et al, 1981; McGrath et al, 1986) and stroke (see above) may have important effects in decreasing blood fluidity: this is especially so in relation to haematocrit elevation, platelet activation and neutrophilia. From the teleological point of view, activation of the sympathetic nervous system is appropriate when the body is exposed to an external stress or physical insult, but the haematological changes need to be associated with adequate responses in perfusion pressure to maintain microcirculatory blood flow. Man has not evolved for this to occur in the presence of a vascular obstruction, with its associated distal hypotension and poor perfusion. It is with this in mind that haemodilution has been advocated in an attempt to achieve by therapeutic intervention what nature is unable to do. It is interesting to remember that the acute/chronic phase response seen in relation to infectious, inflammatory or traumatic insults is associated with a 'compensatory' anaemia (Reizenstein, 1983). With more chronic activation of the organism's response to an injury and the need for healing, blood fluidity is ensured by autohaemodilution while the other cellular and humoral components of the blood involved in the response are activated. A similar situation is seen in normal pregnancy (Hytten, 1985).

MANAGEMENT OF STRESS POLYCYTHAEMIA SYNDROMES

There are broadly two aspects to the management of the relative polycythaemias (Table 2). Firstly, identification and avoidance of precipitating or aggravating factors is important. Secondly, attention must be given to reversing the haemorheological consequences of decreased blood fluidity. This is most important in the acute medical setting, particularly if a vascular episode has already occurred. It is not the subject of this review to consider in detail the numerous methods available for improving fluidity of blood. However, as polycythaemia is the main contributor to hyperviscosity in the stress polycythaemia syndromes, and the red cells are the main determinant of whole blood viscosity, it is logical that haemodilution should be the mainstay of therapy (Gottstein, 1981; Wood and Fleischer, 1982). It is commonly debated whether this should be normovolaemic or hypervolaemic haemodilution. In the light of the mechanisms of the stress polycythaemia syndromes, in which the main pathophysiology involves alterations in cardiovascular control and venous compliance, the terms normovolaemia and hypervolaemia are only relative. The essence of safe haemodilution is to avoid hypovolaemia and hypotension in the presence of threatened blood fluidity. However, haemodilution may be achieved by either venesection with isovolaemic replacement with an appropriate colloid solution, or colloid infusion in conjunction with therapy that will increase venous compliance (e.g. venodilators). Either approach is acceptable as long as cardiac filling pressures/

Table 2. Management of the contracted plasma volume syndromes.

Correct the haemorheological crisis
Rehydration
Plasma volume expansion
Haemodilution
Dextran
Antiplatelet therapy
Identify and correct interacting and aggravating factors
Hypoxia
Sepsis
Hypovolaemia and hypotension
Radiological contrast media
Dehydration
Hypothermia
Hypoglycaemia
Blood transfusion
Identify and remove causes and precipitating factors
Hypoxia
Smoking
Stress
Cold exposure
Alcohol
Neurological disease
Diuretic therapy
Identification of large vessel disease
Specific investigations (if indicated, to confirm the true nature of the polycythaemia)
Red cell mass and plasma volume measurements
Specific therapy (which may assist in expanding the plasma volume)
Antihypertensive therapy, e.g. prazosin
Long-term follow-up

volumes are maintained to achieve adequate cardiac output and blood pressure. The dextrans, antiplatelet agents and anticoagulant therapy may all have a part to play in specific clinical settings.

The treatment of the chronic stress polycythaemia syndromes can be relatively simple in those patients where stressors can be identified and removed. Smoking, psychological stress, intermittent hypoxia, obesity, hypertension, and alcohol are all possible precipitants which may or may not be correctable. Early in management venesection may be indicated, and in cases where precipitants cannot be identified venesection may be the only approach to long-term therapy. Although venesection may seem illogical from a mechanistic point of view in these cases, it does assist in controlling the rheological problem (Humphrey et al, 1980a, 1980b). It could be argued that a more balanced (i.e. normal haematocrit) compensation to contraction of the vascular compartment is achieved by venesection. A common observation in these patients is that venesection may be relatively infrequent (up to three monthly) to maintain a satisfactory haematocrit (personal observation). The patients usually feel better and hypertension, if it is present, frequently settles. These clinical observations may be a subtle clue to

pathogenesis. If potent, long-acting oral venodilating agents were available, they may be particularly valuable in the stress-related contracted plasma volume syndromes. Prazosin and isosorbide dinitrate are drugs which may warrant more attention in this respect (Letcher et al, 1979; Hossman et al, 1981).

HYPOTHESIS

As stress polycythaemia has been the subject of continuing controversy and conjecture over the years, I feel justified in presenting some personal hypotheses and suggestions as to what the future may hold in our understanding of this difficult group of polycythaemias. It is in idiopathic stress polycythaemia where the mechanisms are most poorly understood. In my opinion the idiopathic stress polycythaemia syndromes are a heterogeneous group of disorders with several different aetiologies. In some cases they may represent polycythaemia resulting from activation of the autonomic nervous system as the result of overt or covert psychological stress. This is one of the components of the haematological stress syndrome observed in type A personalities in whom the sympatho-adrenal responses have been shown to be accentuated (De Quattro et al, 1985). Why only some people react in this way is one of the unanswered questions of psychosomatic medicine. However, as already mentioned, there are analogies to be found in our understanding of essential hypertension (Herd, 1984; Horikoshi et al, 1985). Other patients with idiopathic stress polycythaemia in whom psychological stress does not appear to be a factor may have a primary disorder of blood volume regulation.

One could hypothesize that in some patients with a contracted plasma volume syndrome there may be a disorder of the autonomic nervous system or of adrenergic receptor function. There is literature addressing the problem of ageing effects on adrenergic receptors and the autonomic nervous system (Feldman, 1986; Roberts and Steinberg, 1986). β-Adrenergic mechanisms seem more susceptible to ageing than α-adrenergic mechanisms (Martin et al, 1986). If there is an imbalance in autonomic control or atrial receptor/atrial natriuretic factor function, there may be a resetting of the set point for cardiovascular compartment size and venous compliance. This hypothesis would suggest that the idiopathic stress polycythaemia syndromes are disorders of total blood volume control: the haematological response is unbalanced, with the effect mainly manifest in contraction of plasma volume. Supporting this hypothesis is the finding that patients with idiopathic stress polycythaemia may have a red cell mass towards the lower limit of normal (Humphrey et al, 1980b; personal observations). This would suggest that red cell mass has reduced with the plasma volume, but to a lesser extent. On the basis of this hypothesis there could be several points in blood volume control mechanisms which may account for an idiopathic stress polycythaemia syndrome. If this turns out to be the case, the term stress polycythaemia may be inappropriate. Alteration in adrenergic function may be responsible for changing haematocrit with age. Overall there appears to be a gradual fall in haematocrit and blood volume with age, the mechanisms of which remain

unclear. However, there are patients whose haematocrit appears to have elevated with age, for no identifiable reason. At present these patients are classified as relative polycythaemia/stress polycythaemia.

Phaeochromocytoma is a good model for illustrating what happens to blood volume and haematocrit control when there is excessive adrenergic activity. Although relative polycythaemia may be seen in phaeochromocytoma, reduction in total blood volume is more typical. This is predominantly due to plasma volume contraction, but the red cell mass may also be reduced. Pinaud et al (1985) in ten patients with phaeochromocytoma found a mean blood volume of 65 ml/kg with mean plasma volume of 42 ml/kg and reduced red cell mass of 23 ml/kg.

Support for the contention that many cases of stress polycythaemia are due to alteration in venous capacitance is found in the analogous inverse situation of the relative anaemias, where anaemia is due to secondary plasma volume expansion in the presence of a normal red cell mass. Many of these patients are regarded as having dilutional anaemias as a result of increased fluid; however, I would argue that in most of these patients the inverse of the stress polycythaemia mechanism is being observed. Venodilating drugs, e.g. narcotics, anaesthetic agents, nitroprusside and isosorbide dinitrate, may all lead to a fall in the haematocrit level due to expansion in the plasma volume. This may occur without any exogenous fluid having been administered and results from shifting of fluid from the interstitial compartment.

There is good evidence that haematocrit alterations are intimately related to cardiovascular control. In addition there is a wide clinical spectrum of relative anaemia and relative polycythaemia which are predominantly manifestations of these interactions between the cardiovascular system and blood volume. For patients whose haematocrit levels remain within the normal range, even though they may have fluctuated significantly, few questions are asked. However, if the changes in plasma volume result in a patient developing relative anaemia or relative polycythaemia, greater attention is taken, as the patient has entered the abnormal haematocrit range.

SUMMARY

Relative polycythaemia is a general term which includes patients with a normal red cell mass but a contraction of the plasma volume as the cause for the polycythaemia. The relative polycythaemias can broadly be divided into two groups. Firstly, relative polycythaemia may be due to a primary loss of plasma volume due to dehydration, capillary leak or hypo-oncotic pressure. Secondly, relative polycythaemia may be due to a primary contraction of the vascular compartment (i.e. reduced venous compliance). It is this second group which is the least understood and is analysed in detail in this review. In general, this group of polycythaemias is secondary to exogenous or endogenous stress and is mediated via the sympathetic nervous system. Hypoxia, smoking, neurological disorders, myocardial infarction and acute psychological stress have all been demonstrated as possible factors. In many cases of chronic stress polycythaemias aetiological factors may be identified, whereas

in others the term idiopathic is probably appropriate. There appears to be a relationship between the idiopathic stress polycythaemias, hypertension and psychological stress. Other patients may have primarily a disorder of blood volume control involving the autonomic nervous system and its receptors.

The haemorheological significance of relative polycythaemia and its management are discussed. Treatment is generally dictated by the underlying cause. In stress polycythaemias the stimulus should be removed as far as possible. However, in some patients with chronic idiopathic stress polycythaemia, regular venesection may be required to maintain the venous haematocrit at an appropriate level.

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