IS THERE any evidence that the blood volume is regulated? Or, put more specifically, is there any evidence that signalling systems, nervous or hormonal, respond to changes in the optimal level of blood volume and bring into play mechanisms that restore the blood volume to optimal levels? By examining what is known of the factors controlling blood volume we may see if any answer can at present be given to this question.

Table 1 shows that the average healthy adult man has about 2 liters by volume of red cells (in number about $2 \times 10^{13}$) and 3 liters of plasma. In a given healthy adult these values remain fairly constant, rarely varying by more than 5 to 10 per cent about a mean value over periods of weeks or months. Table 1 also shows approximate estimates for the volume of the red marrow. It has been calculated that the red marrow contains about $7 \times 10^{11}$ red cell precursors, or approximately 3 per cent of the number of the circulating red cells. Many of the precursor cells, however, are a good bit larger than the mature red cell, so that, at a guess, we may take the volumes of the red cell precursors in the bone marrow to be about 5 per cent of that of the circulating red cells. This volume is only a small fraction of the red cell volume.

Is there any need for the blood volume to be maintained with any degree of constancy? What would go wrong if it decreased or increased greatly? The function of the circulation is the adequate perfusion of the tissues so that nutrients—gases and solutes—may be delivered and waste products may be removed. For this function the most important parts are the capillaries and the blood perfusing them, and the heart and the larger blood vessels, which pump and distribute the blood to the capillaries, are only servants in this system. It seems probable that the capillaries contain only a small per cent of the circulating blood, although no precise estimates of this quantity have ever been made and, therefore, we can rephrase our question thus: can the heart and the distributing blood vessels maintain an adequate perfusion of the tissues with large changes in blood volume? It is known that withdrawing 500 ml. (about 10 per cent of the blood volume) from an adult man has little effect, and in supine man a reduction of the blood volume by even 15 to 20 per cent may not apparently greatly embarrass the circulation. A reduction of the blood volume by 30 per cent, 1,500 ml., leads to a fall in blood pressure, and by 30 to 40 per cent to a fall in cardiac output and an increase in circulatory resistance, with signs of inadequate tissue perfusion, such as increased blood carbon dioxide and lactic acid content. There is little good evidence on how much the blood volume may be increased without circulatory disturbance. Our own observations show that the blood volume of the

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Regulation of Blood Volume

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This paper is a general account of some of the material in a review by Drs. T. H. Allen, J. E. Roberts and the author.

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rabbit may be increased by 50 per cent over a week or so by dextran infusions, without apparently seriously embarrassing the circulation; but an increase greater than this may lead to pulmonary congestion, pleural effusions, cyanosis, dyspnea, and death on exertion. Patients with congestive cardiac failure rarely show increases in blood volume greater than 1.5 to 2.5 liters. It can perhaps be concluded that circulatory function is little disturbed by changes in blood volume of ± 10 per cent, but is seriously disturbed by reductions of 30 per cent or increases of perhaps 50 per cent. Though this does not suggest that an existing regulation of the blood volume needs to be very precise, it does indicate that the blood volume cannot depart too far from its normal level.

Let us now turn to an examination of some of the controlling mechanisms. First we examine some properties of what may be called "flux systems." These are systems, linked or otherwise, through which there is continuous flow of materials. Figure 1 shows a chain of simple flux systems. Consider the topmost of these. It consists of a tank containing a volume, V₁, of fluid with a tap controlling the inflow, and another tap controlling the outflow. V₁, the volume in the tank, depends on the rates of inflow and outflow. For instance if the inflow remains constant, opening the outflow tap ("outflux 1") further will cause V₁ to decline until a new equilibrium is reached, and reducing the outflow will cause V₁ to increase. If the outflow is held constant, increasing or decreasing the inflow by the "influx" tap will cause V₁ to increase or decrease until new equilibria are reached. Thus, the volume V₁ is controlled by the settings of the taps "influx" and "outflux 1." Now, examine the further degree of complexity obtained when the top tank empties into a second tank, containing V₂ volume of fluid, the outflow from which is governed by tap "outflux 2." What controls the volume of V₂? Clearly taps outflux 1 and outflux 2, but how effective is the former? If outflux 1 is opened fully, we can suppose that the contents of tank 1 rapidly flow into tank 2. This will temporarily increase the volume V₂, but this in turn will increase the outflow through outflux 2, so that V₂ will then start declining, and now the inflow to the second tank is governed by the inflow to the first tank. This illustrates that the real governors of a system in equilibrium such as that of figure 1 are the first inflow and the last outflow taps, provided of course that there is continual flow through the system. Changing the setting of intermediate taps can only have temporary effects.

The red cell volume may be pictured as a flux system contained in a tank, the blood vessels and heart, with an inflow tap from the erythropoietic bone marrow, and an outflow
A possible scheme of the division of the erythrocytic precursor cells in the bone marrow. To avoid the complexities of the various nomenclatures the initial cell in the series is termed the stem cell and cells formed by division from this: generation-1, generation-2, generation-3, and generation-4 cells.

Figure 2

The left side of the figure presents the division of the erythrocyte precursors shown in figure 2. The right side of the figure pictures these divisions as a chain of interlinked flux systems of the kind shown in figure 1. The total numbers of stem cells, and each generation, N1 for G1, N2 for G2, N3 for G3, and N4 for G4, are represented as an occupying a tank. As each cell divides, it leaves the tank it is in and passes to the next tank. This is a pictorial representation of mathematical relations developed elsewhere.1

The formation of red cells in the bone marrow can be represented by something like the events shown in figure 2. Some cell, call it the stem cell, the first in the erythroid series, must divide, and to maintain the supply of stem cells it seems likely that one of the daughter cells, call them generation 1 (G1) cells, must persist as a stem cell, and the other must become a true first-generation cell. The first-generation cell must divide again to form 2 generation-2 cells, these must both divide again to form 4 generation-3 cells, and so on, until finally in this process division ceases and the cells mature through the stage of the reticulocyte by losing their nuclei to become new red cells. Although there has been much study of the morphology of the bone marrow, at present we do not know exactly how many generations there are between the division of the stem cell and the red cell, but a reasonable guess is 4, which would mean that each stem cell division led to the production of 8 red cells. Drs. Allen and Roberts1 have developed equations to describe this system, which are visually presented in figure 3. The left side of the figure pictures the division process as already described. The right side of the figure pictures the results as a train of interlinked flux systems. The first (topmost) tank contains all the stem cells in the bone marrow, and we imagine these as self-replenishing by the unusual division process described above. Of the pair of cells formed by division of these, one passes back into the tank as a stem.
cell, the second becomes a generation-1 (G1) cell and leaves the first tank to enter the second tank, which contains all the G1 cells, N1 in number. The outflow from this tank consists of the generation-2 cells (G2); that is, as soon as the G1 cells divide, they are pictured as leaving the generation-1 tank and entering the generation-2 tank. Note that twice the number of cells leave the generation-2 tank as enter. The G2 cells divide to become G3 cells, so that there is a generation-3 tank with an inflow of divided G2 cells, and finally there is a generation-4 tank. Thereafter, although the red cells change their morphology through the reticulocyte stage, no further division takes place. In the light of our previous discussion 2 points are clear from figure 3. First the governor of the system is the first inflow, the rate of division of the stem cells. Second, though we might expect temporary changes in red cell volume from, say, opening one of the intermediate taps widely, which is equivalent to speeding up the division of an intermediate generation, such an effect can only be temporary, and because of the relatively small volume of the erythropoietic bone marrow, quite small.

Figure 4 shows a regulated flux system, regulated in the sense defined in this symposium. Both inflow and outflow taps are controlled by regulating systems. These are pictured as consisting of a receptor (R), which signals the level of the volume in the system to an integrator (I), where it is compared with an ideal signal, S. The ideal signal in servo-engineering is often termed the goal-setter. The difference between the incoming signal and the ideal signal, E, termed the "error" in servo-engineering, then activates an effector, M, pictured in figure 4 as a servomotor, which turns the inflow or outflow tap, or both, to change the volume to a more optimal level. Can we fit our present knowledge of the regulation of the red cell volume into such a system? Our discussion has ruled out the outflow tap as being in any way a precise controller, and has shown that the prime regulator of the inflow, M, the servomotor shown, must be the rate of division of the stem cells.

REGULATION OF A FLUX SYSTEM

Figure 4

A regulated flux system. The regulation of inflow and outflow is pictured as controlled by servomechanisms. Each of these consists of a receptor mechanism, R, which senses the volume of fluid in the tank. This signals an integrator, I, which compares the signal with an ideal signal from a goal-setting mechanism, S. The resulting integrated output from the integrator, the "error," E, then activates an effector system, M, pictured as a servomotor, which controls the setting of the tap.

This suggests that the error system works through some humoral cell growth and division factor. Evidence partially supports this. Thus, it has long been known that exposure of a mammal to low oxygen tension results in an increase in red cell volume. For instance, moving adult men from sea level to 15,000 feet leads to an increase in red cell volume over some months to some 1.5 times the initial level. Clearly the stem cell tap must have been widely opened, since no change occurs in the length of red cell life. If one member of a pair of surgically joined rats (parabiotic rats) is exposed to a low oxygen tension, not only the red cell volumes but also the bone marrows of both animals show the changes expected on exposure to low oxygen tension, strongly suggesting the liberation of a humoral growth factor. In the last few years much work has been done on such factors, the so-called erythropoietins; but much of this work is incomplete because the effects of supposed hormones on the stem cell system have

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not been studied. We can at present only conclude that the controller, M, of the inflow tap is probably some hormone or hormones. What however of the sites and nature of the receptors that signal the state of the red cell volume, and the nature of the integrating device and the goal-setter? Of these we are at present entirely ignorant.

Let us now turn to the question of the regulation of the plasma volume, which in health forms the other three fifths of the circulating blood volume. For clarity we shall first develop a model of the factors controlling the plasma volume and then discuss whether there is regulation of the plasma volume acting through some of these controls. The remainder of the controlling systems falls into the province of Dr. Elkinton’s paper.

First, 93 per cent of the volume of plasma is water, and we therefore disregard the other 7 per cent made up of the plasma proteins, and fats. We require a model, that is a simplified picture, preferably capable of mathematical expression, of the factors responsible for the level of the plasma volume. The body water can be divided into plasma water, interstitial water, and cell water, and the upper part of figure 5 shows the elements of a model, consisting of 3 tanks, representing plasma water, \( V_p \), interstitial water, \( V_i \), and cell water, \( V_c \), joined together by siphons, with a flux passing through the plasma water tank. The inflow is primarily from the alimentary tract and the controlled outflow chiefly through the kidneys, though water loss also occurs through the skin and lungs. The tanks are not drawn to scale, and there is relatively much less plasma water and more cell water than shown. Also, for the tanks to be anything like the body water there must be a continuous rapid exchange through the siphons in both directions. For we know that labeled water introduced into the body rapidly exchanges with all the body water, primarily by carriage in the circulation and diffusion through the tissue fluids and cells.

The lower part of figure 5 shows further details of the model. First, semipermeable membranes have been placed between the plasma and the interstitial fluids, \( M_{cap} \) (to represent the capillary membrane) and between the interstitial and cellular fluids, \( M_{cell} \) (to represent the cellular membranes). The capillary membrane allows free passage of water and salts and very slow passage of the proteins; the cell membrane allows, we suppose, only free passage of water, other substances passing across it requiring ‘active transport.’ Next, solutes have been added, large solutes—the colloids,—shown by C’s, and smaller solutes,—the crystalloids—shown by s’s. The main crystalloids in the extracellular fluids (the plasma and interstitial fluids) are the sodium salts of chlorides and bicarbonates, and the main colloids, the plasma proteins, which are on the average 3 to 5 times more concentrated in the plasma than in the interstitial fluid. The main crystalloids in the cellular fluid are potassium and magne-

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sium salts, but little is known of the cell colloids. The body fluids are not all at the same pressure. This is particularly true for the plasma, which is exposed to a series of pressure gradients generated by the action of the heart and the distensibility of the blood vessels. In the model the only pressure considered is the average pressure at the capillary membranes, and this is pictured in figure 5 as generated by a pressure system (for instance a tank of compressed air) and measured by a pressure gage. A final point about the model needs emphasizing: the distribution of water in the tanks depends on the distribution of the colloids and colloids through their effects on the rate of diffusion of water. Thus, suppose more solute is added to one of the tanks and the membrane separating it from the next tank impedes the passage of the added solute. Then the added solute will reduce the rate of diffusion of the water to which it has been added, and water will diffuse inwards more rapidly than it diffuses outwards, until either a restraining pressure is developed, the osmotic pressure, or eventually the solutes are evenly distributed among the tanks. (This is only strictly true if Donnan forces are negligible.) In either case at equilibrium the rates of diffusion across the membrane will be equal in both directions.

Examining figure 5, we can now come to certain conclusions about the factors controlling plasma volume. 1. The volume of plasma water will depend on the quantity of the total body water, which must be controlled chiefly by the rates of inflow and outflow through the gut and kidney. 2. For a given quantity of body water, the volume of plasma water must depend on the factors controlling the distribution of water among the 3 tanks. These are (2a) the capillary pressure—a higher pressure will displace water out of the plasma tank by increasing the outward diffusion rate; (2b) the plasma colloid—secretion of more protein into the plasma will counteract water outflow to the other compartments by reducing the rate of water diffusion outward; (2c) the quantities of crystalloid solutes in the extracellular and cellular fluids. For instance, it can be shown experimentally that introduction of hypertonic saline into the plasma leads to passage of water from the cells into the extracellular fluids. Factors (2a) and (2b) it will be remembered were proposed by Starling many years ago.

Dr. Elkinton in the following article deals with the control of (1) and (2c). It may be noted that the quantities of crystalloid solutes in the body depend on crystalloid inflow and outflow in the same way as body water depends on water flux; the distribution of crystalloid solutes in the body depends on cellular activity as is shown by the redistributions that occur on cell death. Certain of the colloids, for instance, sodium in the bones, also exist in stores in the body so that the quantity in the body fluids can be modified by release from or deposition in the stores, though little is known of the control of such exchanges.

Dealing with the remaining factors, we cannot at present say whether any regulation of mean capillary pressure or of plasma colloid osmotic pressure (protein concentration) exists. Something has been learned of the factors controlling the total quantity of circulating plasma proteins. Eighty to ninety percent of the plasma proteins, that is essentially all but the immune gamma globulins, are synthesized in the liver. Synthesis is continual as is breakdown, so that, as with the red cells, the total quantity of a given plasma protein can be pictured as part of a flux system, with continual inflow from the liver and outflow to the breakdown site. In an adult man about 10 Gm. of albumin is made and broken down a day, and it can be calculated that a single liver cell makes about 5,000 albumin molecules per second. It seems likely that the amino acids, which are joined together to make these proteins, are assembled on nucleic acid protein “assembly lines” and that these form part of a network through the cell known as the endoplasmic reticulum.11 The sites of plasma protein breakdown and the factors controlling the rate of breakdown

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are incompletely known, but some of our own experiments suggest that breakdown is relatively constant. Hence, it is possible that any existing regulation is of synthesis. Presumably the rate of synthesis of albumin will depend on the total number of albumin-synthesizing liver cells and the average number of albumin assembly lines in them. Thus, the rate of synthesis could depend on cellular growth factors and factors determining the size of the nucleic acid protein production lines. There is good evidence of the potentiality of the liver cells to multiply. For instance, after partial hepatectomy, when the total quantity of circulating plasma proteins starts to fall, the remaining liver cells increase their mitotic rate, the ribose nucleic acid content of the cells increases, and, in the rat at least, the bulk of the lost liver has been restored in a few weeks. If a partial hepatectomy is performed on one rat of a para-biotic pair, an increased mitotic rate is seen in the liver cells of the other animal, suggesting that a hormonal growth factor is active. But this essentially is as far as our knowledge goes; and, as with the red cell, we cannot say whether the total quantity of any, or all, of the plasma proteins is truly regulated in the defined sense of this word.

So far little convincing evidence has been found for regulation of the red cell or plasma volumes. But, to conclude, we note briefly 2 reflexes that appear to be regulatory, though their importance is at present uncertain. The walls of the right and left atria are supplied with a rich nerve network containing nerve terminals similar to those in the carotid sinus. According to Henry and collaborators\textsuperscript{14} stretch of the left atrium, as by distention of an indwelling balloon, leads to production of afferent impulses that pass to the hypothalamus via the vagi and there inhibit the release of the antidiuretic hormone, so leading to a water diuresis. Farrell\textsuperscript{15} suggested that stretch of the right atrial receptors evokes afferent impulses that lead to the inhibition of the release of another hormone from the diencephalon, which in turn regulates the secretion of aldosterone by the adrenal gland. This might result in some increased loss of sodium chloride from the body. These stretch receptors in the atria are in direct relation, through the atrial tension, with the volume of blood in the atria, and it has been suggested that this volume varies directly as the volume of blood in the great veins and low-pressure portion of the cardiovascular tree.\textsuperscript{16} After integration in the central nervous system the error signal is transmitted by hormones acting on the kidney, that is on the outflow taps.
of the water and salt flux systems. The controlling devices are pictured in servomechanism terms in figure 6. As shown, the kidney consists of a complex outflow tap. One servomotor, \( M_1 \), controls the rate of glomerular filtration, and the second, \( M_2 \), the rate of tubular reabsorption. The reflexes are both believed to act by hormones on the second servomotor, \( M_2 \). Though evidence indicates that the first effector, \( M_1 \), is of great importance,\(^{17}\) we at present are almost entirely ignorant of its regulation.

**Summario in Interlingua**

Le question de si o non il existe un sistema regulatori del volumine de sanguine es precisate per le autor in le forma del question de si o non il existe systemas de signales—de character nervose o hormonal—que respondes a deviationes ab le nivello optimal del volumine de sanguine per activar mechanismos que servi a restaurar le volumine de sanguine a su nivello optimal.

In su analyse de iste question, le autor comencia per describer le factores de que le volumine de sanguine depende, tractante separatamente le mechanismos que provide (1) le volumine erythrocytic e (2) le volumine del plasma.

Le responsa al question inicial consiste in le conclusion que il existe a iste tempore certe indicios que pote justificar le supposition del existentia de un sistema de regulation hormonal del volumines erythrocytic e plasmatic sed que extense recercas additional va esser requirite pro transformar ille supposition in un facto demonstrate.

**References**

SYMPOSIUM ON REGULATION OF THE CARDIOVASCULAR SYSTEM IN HEALTH AND DISEASE: Regulation of Blood Volume
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