CIRCULATION: OVERALL REGULATION 1072

ARTHUR C. GUYTON, THOMAS G. COLEMAN, AND HARRIS J. GRANGER[1,2]

The Department of Physiology and Biophysics, University of Mississippi School of Medicine, Jackson, Mississippi

This article is an experiment, one undertaken primarily because of the long-term belief of Dr. Victor Hall, Editor of the *Annual Review of Physiology* for many years, that physiology is, or at least should be, an analytical subject, and that a method not utilized to its fullest advantage for organizing review material is the systems analysis. Furthermore, one of the most likely areas in physiology for which a systems analysis could be of value would be in a discussion of circulatory regulation. Therefore, this article was undertaken directly at the request of the editors of the *Annual Review of Physiology* to attempt the welding together of a systems analysis of circulatory regulation with a review of the current literature in this field.

The systems analysis of circulatory regulation developed for this article is based on earlier, much less extensive analyses (Guyton & Coleman 1, 2); it is illustrated in Figure 1. This analysis is comprised of 354 blocks, each of which represents one or more mathematical equations describing some physiological facet of circulatory function. In general, each of the functional blocks has been the subject of research investigation by one or many investigators, but the analysis is based on cumulative knowledge of the circulation rather than simply on current literature. Therefore, the analysis presented here is not a review of the current literature but is a framework to show how the different regulations operate together in the overall system. Later in this review we will attempt to show some of the voids still present in our knowledge of circulatory regulation (which is perhaps the most important value of performing systems analyses), and we will discuss the current research that is attempting to fill these voids.

A criticism that has often been made against systems analyses, and very justly so, is that they are usually designed to explain specific phenomena. Therefore, they too often are based on such bizarre concepts of function that they not only fail to give correct predictions (other than the specific ones for which they are designed) but, indeed, often give exactly reverse predic-

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tions. Therefore, the analysis of Figure 1 was based almost entirely on actual experimental data, and it has been tested in computer simulations to see whether or not it can predict the animal or human results of many different types of circulatory stresses induced either experimentally or as the result of clinical abnormalities. Figures 2 through 5 present simulations of some of these experiments or clinical conditions. They will be described later in the article.

BRIEF DESCRIPTION OF THE SYSTEMS ANALYSIS

For someone familiar with the principles of systems analysis, most of the present analysis can be understood by studying Figure 1 and its legend, which includes (*a*) definitions of the symbols used in the systems analysis and (*b*) units used in the analysis. However, the following brief description will give other helpful information for understanding the overall function of the analysis.

As illustrated in Figure 1, the analysis is divided into 18 different major systems that enter into circulatory control. Within each of these major systems are often several subsystems. The systems, their block numbers, and brief discussions of their components are given in the following few paragraphs.

1. *Circulatory dynamics* (*blocks 1 through 60*).—Blocks 1 through 33 represent the pathway of blood flow around the circulation, beginning with aortic pressure (*PA*) and returning to excess filling volume of the aorta (*VAE*) above that value which can be held by the aorta at zero pressure. The circuit is divided into five different volume segments: the aorta, the veins, the right atrium, the pulmonary arteries, and the combination of pulmonary veins and left atrium. Flow from each of these respective segments to the next segment is calculated by dividing pressure difference by resistance; the volumes are integrated with respect to time; and the volume of filling in each segment determines the pressure in that segment.

Other blocks in the circulatory dynamics portion of the analysis are: blocks 34 through 38 to calculate the resistances to blood flow respectively through the muscle vasculature and through the non-muscle, non-renal vasculature; blocks 39 through 43 to calculate venous resistance; block 44 to calculate the resistance between the large veins and the right atrium; blocks 45 through 48 to calculate the interaction of left ventricular function on right ventricular function; blocks 49 through 51 to calculate the effects of right ventricular muscle strength, autonomic stimulation, hypertrophy of the heart, deterioration of the heart, and pulmonary arterial pressure on the output of the right ventricle; blocks 52 through 57 to calculate pulmonary resistances; blocks 29, 58, and 59 to calculate the effects of sympathetic stimulation, cardiac deterioration, cardiac hypertrophy, left ventricular muscle strength, and the loading effect of aortic pressure on the output of the left ventricle; and block 60 to calculate the change in filling of the vascular system as the blood volume changes.

2. *Vascular stress relaxation* (*blocks 61 through 65*).—The control factors of stress relaxation are the sensitivity of the mechanism, set by the value *SR*, and the excess volume of blood in the veins (*VVE*). The output of this circuit is additional vascular volume that is added to that of the circulatory circuit (*VV7*).

3. *Capillary membrane dynamics* (*blocks 66 through 82*).—Blocks 66 and 67 calcu-

late capillary pressure. Blocks 68 and 69 calculate fluid leakage from the capillaries, and blocks 70 through 72 calculate the rate of change of fluid volume in the plasma, plasma volume, and blood volume. Blocks 73 through 76 calculate loss of protein from the capillaries, including the "stretched pore phenomenon." Blocks 77 and 78 calculate hepatic formation of protein, and blocks 79 through 82 calculate total plasma protein and plasma colloid osmotic pressure.

4. *Tissue fluids, pressures, and gel (blocks 83 through 113).*—Blocks 83 through 85 calculate total tissue fluid volume and total tissue pressure. Blocks 86 through 88 calculate free interstitial fluid volume, solid tissue pressure, and pressure of the free interstitial fluid. Blocks 89 through 92 calculate recoil effects of the gel reticulum (*PRM*) and the pressure caused by this (*PGH*). Blocks 93 through 99 calculate the balance of pressures at the interface between free interstitial fluid and fluid in the gel phase of the tissue fluids. Blocks 100 and 101 calculate gel volume. Blocks 102 through 105 calculate free interstitial fluid protein, its concentration, and its colloid osmotic pressure. Blocks 106 through 108 calculate lymph flow and return of protein in lymph to the circulation. Blocks 109 through 113 calculate transfer of protein into or out of the tissue gel, total protein in tissue gel, and concentration of protein in tissue gel.

5. *Electrolytes and cell water (blocks 114 through 135).*—Blocks 114 and 115 calculate extracellular fluid volume and total body water. Blocks 116 through 119 calculate accumulation of sodium in the extracellular fluids and concentration of sodium. Blocks 120 through 126 calculate extracellular fluid potassium, quantity and concentration, and also rate of potassium excretion by the kidney. Blocks 127 through 132 calculate accumulation of potassium in the cells and its intracellular concentration. Blocks 133 through 135 calculate transfer of fluid through the cell membrane and also intracellular fluid volume.

6. *Pulmonary dynamics and fluids (blocks 136 through 152).*—Blocks 136 through 138 calculate pulmonary capillary pressure. Blocks 139 through 143 calculate volume of pulmonary free fluid and pressure of the free fluid in the interstitial spaces. Blocks 144 and 145 calculate rate of pulmonary lymph flow. Blocks 146 through 151 calculate protein accumulation in the free fluid of the lungs, total protein, and its colloid osmotic pressure. Block 152 calculates rate of protein return in the pulmonary lymph.

7. *Angiotensin control (blocks 153 through 163).*—Block 153 calculates control of angiotensin formation as a function of renal blood flow. Blocks 154 and 155 calculate the effect of sodium concentration on angiotensin formation. Blocks 156 through 163 calculate first, angiotensin concentration (*ANC*) and then the angiotensin effect on other functions of the body [called "angiotensin multiplier" (*ANM*)] and expressed as a ratio of normal function.

8. *Aldosterone control (blocks 164 through 174).*—Blocks 164 through 167 calculate the effects of arterial pressure, potassium to sodium ratio, and angiotensin on aldosterone secretion rate. Blocks 168 through 170 calculate the accumulation of aldosterone in the tissues and its concentration. Blocks 171 through 174 calculate the "aldosterone multiplier" (*AM*) which represents the functional effect of aldosterone in the body in proportion to its normal effect.

9. *Antidiuretic hormone control (blocks 175 through 189).*—Blocks 175 through 182 calculate the total effect on antidiuretic hormone secretion of extracellular ion concentration (represented by *CNA*), of right atrial pressure, and of autonomic stimulation. Blocks 183 through 189 calculate the rate of secretion of antidiuretic hormone and antidiuretic hormone multiplier expressed as the functional effect of antidiuretic hormone in ratio to its normal effect.

10. *Thirst and drinking (blocks 190 through 194).*—Blocks 190 and 191 calculate the effect of central nervous system stimulation on thirst and drinking, assuming that the same drives that affect thirst and drinking also affect the secretion of antidiuretic hormone. Blocks 192 and 193 calculate the effect of tissue ischemia (hypoperfusion states) on salt and water intake. These combine together in block 194 to control overall thirst and drinking.

11. *Kidney dynamics and excretion (blocks 195 through 222).*—Blocks 195 through 200 calculate renal resistances and the effects of autonomic stimulation and blood viscosity on these. Blocks 201 through 207 calculate the effects of arterial pressure, renal resistances, and plasma colloid osmotic pressure on glomerular pressure, filtration pressure, glomerular filtration rate, and renal blood flow. Blocks 208 through 211 represent feedback control of afferent arteriolar resistance in response to flow of fluid through the tubular system (presumably acting through the macula densa and juxtaglomerular apparatus). Blocks 212 through 217 calculate the effects of glomerular filtration rate, degree of renal damage (*REK*), antidiuretic hormone, and aldosterone on tubular reabsorption. Block 218 subtracts tubular reabsorption from glomerular filtration rate to calculate rate of urine output. Blocks 219 through 222 calculate the effects of rate of urinary output, aldosterone secretion, and natriuretic factor on sodium excretion.

12. *Muscle blood flow control and* P_{O_2} *(blocks 223 through 254).*—Blocks 223 and 224 calculate the effect of pulmonary free fluid on arterial oxygen saturation. Blocks 225 through 232 calculate the effects of hematocrit, arterial oxygen saturation, and muscle blood flow on concentration of oxygen in arterial blood, concentration in the muscle venous blood, and muscle venous P_{O_2}. Blocks 233 through 237 calculate diffusion rate of oxygen from the capillaries into the muscle cells. Blocks 238 through 240 calculate accumulation of oxygen in muscle cells and the muscle cell P_{O_2}. Blocks 241 through 244 calculate the effect of muscle cell P_{O_2} on rate of oxygen consumption by the cells. Blocks 245 through 247 calculate the effects of autonomic stimulation on muscle cell utilization of oxygen. Block 248 calculates the rate of oxygen utilization by the muscle cells of the body. Blocks 249 through 254 calculate the vasodilating effect (*AMM*) of muscle capillary P_{O_2} (*PVO*).

13. *Non-muscle oxygen delivery (blocks 255 through 272).*—Blocks 255 through 261 calculate the effects of arterial oxygen concentration, non-muscle non-renal blood flow, and hematocrit, on non-muscle, non-renal venous oxygen concentration and venous oxygen P_{O_2}. Blocks 262 through 265 calculate the effect of capillary P_{O_2} (*POV*) and cell P_{O_2} (*POT*) on diffusion of oxygen from the capillaries to the cells. Blocks 266 through 270 calculate the effect of cell P_{O_2}, autonomic stimulation, and basic rate of oxygen consumption by the tissues on the actual rate of oxygen consumption by the tissues. Blocks 271 and 272 calculate the accumulation of oxygen in the cells and the cell P_{O_2}.

14. *Non-muscle, non-renal local blood flow control—autoregulation (blocks 273 through 290).*—Blocks 273 through 278 calculate the effect of capillary P_{O_2} (*POV*) on rapid autoregulation of blood flow (*AR1*), with a time constant of one minute (*A1K*). Blocks 279 through 283 calculate the time course and the degree of intermediate autoregulation, with a time constant of 20 minutes. Blocks 284 through 289 calculate the effect of long-term vascular changes (for instance, changes in vascularity) on local blood flow control, with a time constant of 11,520 minutes. Block 290 calculates the overall effect of short, intermediate, and long-term local blood flow controls on non-muscle, non-renal, vascular resistance (*ARM*).

15. *Autonomic control (blocks 291 through 320).*—Blocks 291 and 292 calculate the effects of arterial pressure and non-muscle, non-renal P_{O_2} on autonomic function. Blocks 293 through 297 calculate the effects of exercise and of muscle metabolism on autonomic function. And block 298 sums these effects with those of arterial pressure and non-muscle P_{O_2}. Block 299 calculates chemoreceptor output. Blocks 300 through 305 calculate baroreceptor output, including baroreceptor adaptation. Block 306 calculates the output resulting from ischemia of the CNS. Blocks 307 through 311 calculate the summation of total autonomic output expressed as a positive effect for sympathetic output and negative effect for parasympathetic output, and with a time constant of approximately 10 seconds controlled by *Z8*. Blocks 312 and 313 calculate the effects of autonomic stimulation on vascular compliance. Blocks 314 and 315 calculate the effects of autonomic stimulation on the heart. Blocks 316 and 317 calculate the effects of autonomic stimulation on peripheral arteriolar vasoconstriction. Blocks 318 through 320 calculate the effects of autonomic stimulation on venous vasoconstriction.

16. *Heart rate and stroke volume (blocks 321 through 328).*—Blocks 321 through 323 calculate the effects of autonomic stimulation and right atrial pressure on heart rate. Blocks 324 through 326 calculate the effects of cardiac deterioration on heart rate, and block 327 calculates heart rate itself. Block 328 calculates stroke volume output.

17. *Red cells and viscosity (blocks 329 through 339).*—Blocks 329 through 333 calculate the effect of tissue P_{O_2} on the rate of red blood cell production, and also calculates red cell destruction, accumulation of red cells in the blood, and red cell volume. Blocks 334 and 335 calculate hematocrit. Blocks 336 through 339 calculate blood viscosity expressed in terms of ratio to that of normal blood.

18. *Heart hypertrophy or deterioration (blocks 340 through 253).*—Blocks 340 through 344 calculate the effect of systemic arterial pressure and basic strength of the left ventricular muscle on hypertrophy of the left ventricle with a time constant of 57,600 minutes. Blocks 345 through 349 calculate the effects of pulmonary arterial pressure and basic strength of the right ventricular muscle on right ventricular hypertrophy, with a time constant of 57,600 minutes. Blocks 350 through 352 calculate the effect of diminished tissue P_{O_2} on deterioration of the heart.

Overall comment on the systems analysis.—An important factor that allows a systems analysis such as this to predict actual function with good accuracy is the extreme stability of the actual circulatory control system. Because of this stability, the function of any single block, or of any single control mechanism, can be in error as much as $\pm 50\%$ (sometimes even more than this) without significantly affecting the overall output of the system. To give an example, simulated removal of $\frac{3}{4}$ of the mass of the kidneys, thereby depressing all renal functions to $\frac{1}{4}$ normal, causes less than 1% change in body fluid volumes (after all compensations have taken place) and causes only 7 mm Hg rise in arterial pressure. Obviously, the goal of the systems analysis is to be as accurate as possible, but another byproduct of such an analysis is to demonstrate the beauty of the built-in compensations when any one or even a significant combination of its parts is functioning very abnormally. If it were not for the extreme stability of the overall circulatory control system, we would have to know far more basic physiology to make such a systems analysis as this work.

Solution of the systems analysis on a computer.—To simulate overall function of the circulatory system, and particularly to simulate dynamic changes in circulatory function when a stress is introduced into the circulatory system, one can solve the systems analysis of Figure 1 on any computer that is large enough to handle it. The solution requires 16K words of memory for solution in the FORTRAN language on the PDP-9 computer (others may require more). One of the principal problems in such a solution is the fact that some of the control and hemodynamic systems operate with very short time constants (as low as 0.005 min for some points in the hemodynamic circuit) while others operate with tremendously long time constants (as high as 57,600 min for the hypertrophy effect on the effect of the ventricles). In an iterative solution of the analysis without using special computational techniques, the time for computation on the computer could be as great as 100 times real time. However, by computing the rapid time constant factors until equilibrium is reached and then computing the slower time constant factors, it is possible to speed the solution to almost 1/1000 real time.

SIMULATION OF THE EFFECTS OF SPECIFIC CIRCULATORY STRESSES ON CIRCULATORY CONTROL

Simulation of the development of hypertension in a salt loaded, renal deficient patient.—Figure 2 illustrates a cathode ray display of the sequential events during development of hypertension in a simulated patient who was subjected to two abnormalities. Firstly, renal mass was decreased to 0.3 normal and, secondly, the salt load was increased to 5 times normal. These changes were made at the point where the curves begin to break. The curves illustrate the simulated effects, from top to bottom, on extracellular fluid volume, blood volume, degree of sympathetic stimulation, cardiac output, total peripheral resistance, arterial pressure, and urinary output. The time period for the abscissa was two weeks. Note that the instantaneous change was a decrease in urinary output to 0.3 normal. This was followed by slight increases in extracellular fluid volume and blood volume and a simultaneous increase in cardiac output, with less increase in arterial pressure. The increase in arterial pressure that did occur initiated a baroreceptor reflex with resultant depression of sympathetic activity. This decreased sympathetic activity, combined with the vascular stretching effect of the elevated arterial pressure dilated the peripheral blood vessels so that the total peripheral resistance fell below normal for the first few days. Therefore, all the initial increase in arterial pressure was caused by increased cardiac output and not by increased total peripheral resistance.

For the first few days of the simulated experiment, the cardiac output continued to rise, while total peripheral resistance remained below normal. However, at the end of two days the total peripheral resistance returned to normal. By this time the arterial pressure had already risen to approxi-

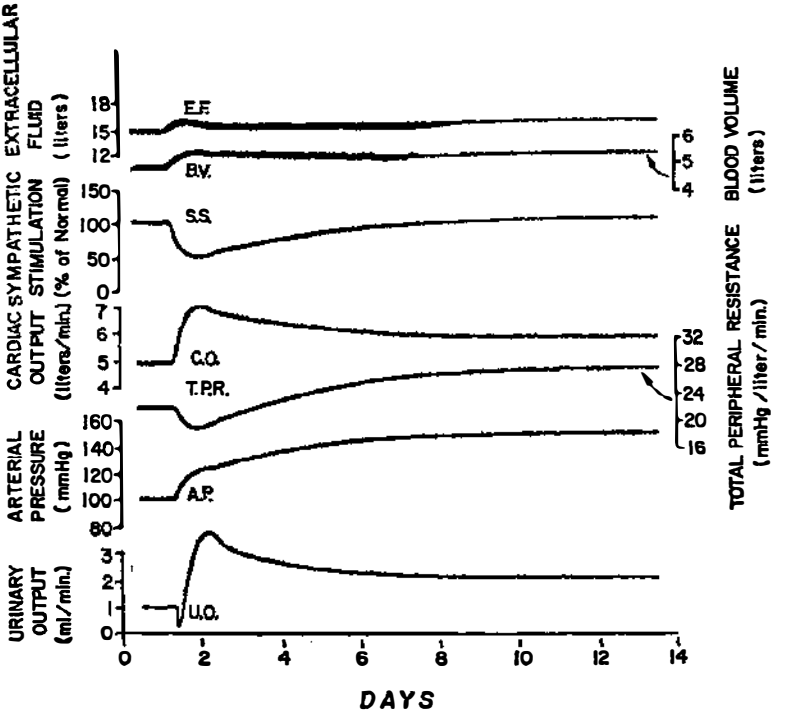

FIGURE 2. Simulation of changes in circulatory function at the onset of hypertension caused by reduction of renal mass to $\frac{1}{3}$ normal and simultaneous increase in salt intake to five times normal. The changes were made at the point where the curves begin to break.

mately 2/3 as high as it would rise by the end of the experiment. During the subsequent days the cardiac output fell toward normal, while total peripheral resistance rose progressively and became the factor that eventually maintained the elevated arterial pressure. In the systems analysis, this shift from increased cardiac output to increased total peripheral resistance was caused by two factors: adaptation of the baroreceptors and long-term control of local blood flow in which excess blood flow through the tissues cause progressive constriction of the blood vessels until the flow returns to normal. Two other significant events were: (*a*) the initial overshoot in blood volume and extracellular fluid volume with return of both of these almost to normal by the end of ten days to two weeks, and (*b*) the increase in urinary output to considerably above normal, despite decrease in renal mass, caused by the effect of the high salt intake on the thirst mechanism.

This test of the circulatory systems analysis was performed because all

of the details of the transient changes in circulatory function during onset of this type of hypertension have recently been recorded in detail both in experimental animals and in patients whose kidneys are either damaged or whose kidneys have been actually removed and in whom the extracellular fluid volume has been expanded artificially for chronic periods of time (Ledingham 3, Coleman & Guyton 4, Coleman et al 5). All of the transient effects shown in the above simulation actually occur in almost exact quantitative and temporal correspondence, including the initial decrease in total peripheral resistance, the initial increase in cardiac output with subsequent return toward normal, the high urine output in salt-loaded animals or patients whose renal function is depressed, the transient but quantitatively small increases in blood volume and extracellular fluid volume, and the decrease in sympathetic activity or increase in parasympathetic activity as evidenced by about 40% reduction in heart rate during the onset phase of the hypertension.

Simulation of congestive heart failure.—Figure 3 illustrates the effects of simulated heart failure over a period of two months. The curves of the figure (listed from top to bottom) show changes in plasma volume, left atrial pressure, right atrial pressure, cardiac output, free fluid volume in the lungs, aortic pressure, extracellular fluid volume, and urinary output. The total time is *nine* weeks. At the first break in the curves, the pumping capabilities of both ventricles were reduced (reduction of all segments of the ventricular function curves) to 0.3 their normal values, and evidences of heart failure ensued. However, recovery of the heart caused many of the evidences of heart failure to disappear. At each subsequent break in the curves, the pumping capability of the heart was decreased approximately another 30% below its value immediately before the break. Eventually the failure was so severe that the simulated person developed severe congestion in the lungs, low cardiac output, and peripheral edema leading to death.

Note the instantaneous decrease in urinary output at the onset of the first heart attack, with urinary output remaining for about one day at about 300 ml/day, the obligatory level of ouptut, until there was beginning evidence of recovery from the heart attack. Note also the instantaneous marked decrease in both cardiac output and arterial pressure, with recovery within minutes of both of these to levels only 10 to 20% below normal despite the severe reduction in the capability of the pump. These initial effects were followed rapidly by increasing extracellular fluid and plasma volumes, and the initial slight increases in atrial pressures increased still more as fluid volume accumulated. However, during subsequent days, as the heart recovered from the attack, all the abnormal effects returned toward normal.

With subsequent attacks the simulated person went though similar repeated episodes until, finally, recovery was insufficient to return the person to a compensated state. The left atrial pressure became so high that the

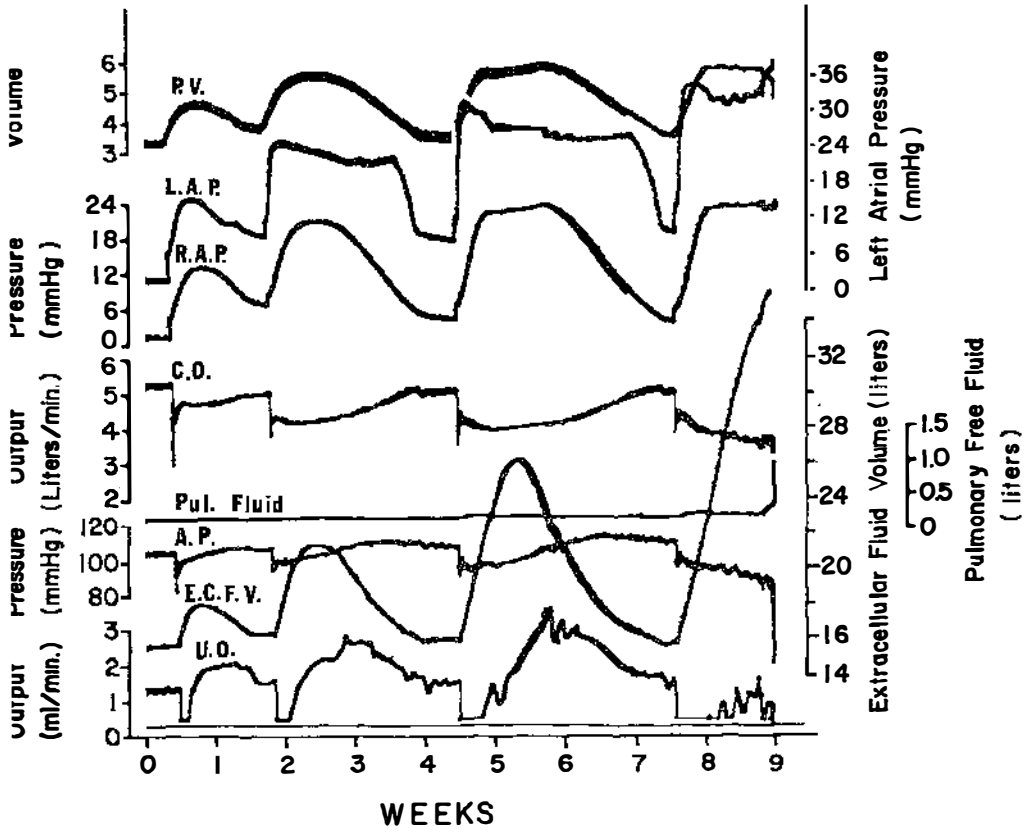

FIGURE 3. Simulation of development of congestive heart failure. At the point where the curves first began to break, the pumping capabilities of both the left and right ventricles were decreased to 0.3 normal. At each of the subsequent breaks in the curves, the pumping capabilities of the ventricles were reduced approximately an additional $\frac{1}{3}$ below the pumping capabilities at that time. The heart recovered partially between each of the attacks. Note at the end of the record that free fluid in the lungs increased suddenly during the last few hours of life, and this increase in pulmonary fluid was the immediate cause of death.

volume of free fluid in the lungs began to rise drastically during the last hours of life. Also, not shown in the record, the oxygen saturation of aortic blood fell below the 50% level, and it was at this point that death occurred.

The events simulated in Figure 3 are almost identical with those that occur in actual cases of progressive cardiac failure, with transient episodes

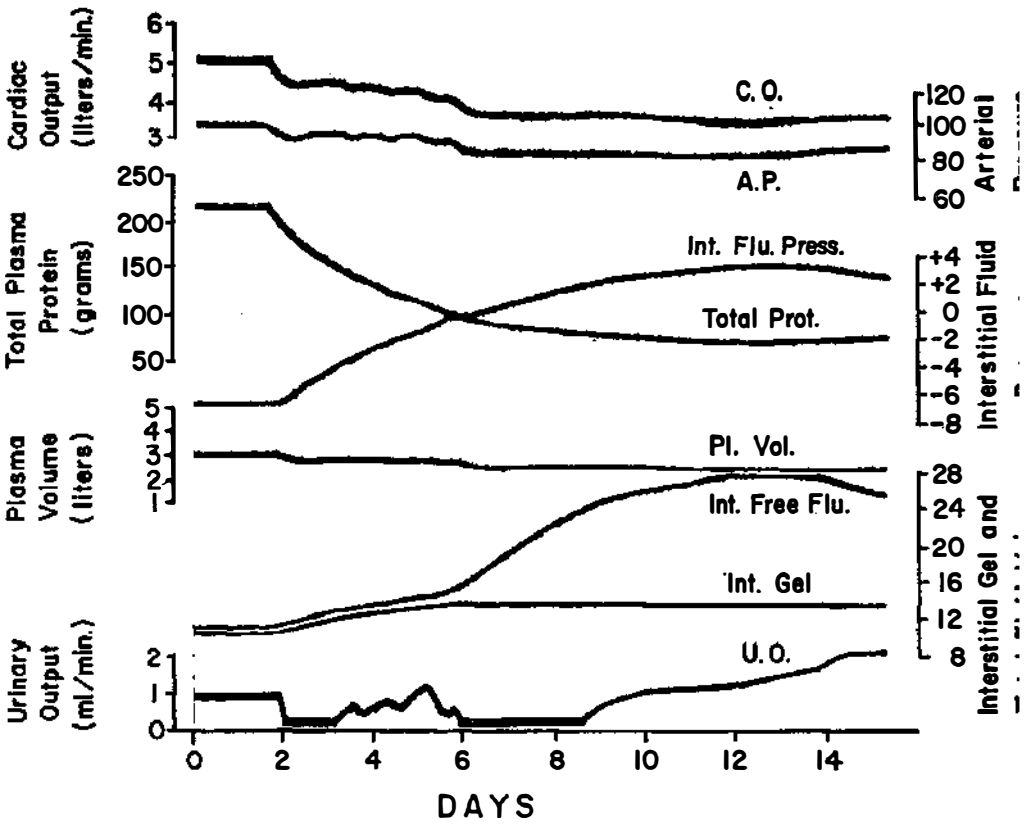

FIGURE 4. Simulation of circulatory changes in nephrosis. At the initial break in the curves, the kidneys began to excrete large amounts of plasma protein, as evidenced by the fall in total circulating plasma protein. Note the tremendous increase in interstitial free fluid when the plasma total protein fell below a critical level. At the end of the record an extremely minute increase in total plasma protein caused marked diuresis and beginning resorption of the edema, a well known characteristic of the disease.

of edema following acute attacks and final entry into a severe stage of congestion and cardiac decompensation, followed by typical pulmonary congestive death.

Simulation of nephrosis.—The principal effect of nephrosis is loss of protein in the urine, which may or may not be associated with significant changes in other functions of the kidneys. Figure 4 illustrates simulated nephrosis in which there was only loss of protein. The different factors displayed in the simulation are (from top to bottom) cardiac output, arterial

pressure, total plasma protein, interstitial fluid pressure, plasma volume, total interstitial fluid volume, volume of fluid in interstitial gel, and urine output. Total time is two weeks. Note also that the space between the total fluid volumes and that of the interstitial gel represents the volume of interstitial free fluid. The initial effect, once the state of nephrosis was instituted, was a progressive decrease in total plasma protein, as illustrated by the declining curve in the figure. This was followed soon by slight decreases in both arterial pressure and cardiac output, marked decrease of urinary output while fluid was collecting in both the free and gel portions of the interstitial fluid, slight decrease in plasma volume, and beginning rise in interstitial fluid pressure. The increase in interstitial fluid pressure continued almost in inverse proportion to the decrease in plasma protein. On the other hand, the interstitial fluid volumes increased moderately at first and then did not increase greatly thereafter until a critically low level of plasma protein (about 0.3 the normal level) was reached. At that point, there was an abrupt rise in total interstitial fluid volume. It was at this same time that the interstitial fluid pressure rose from a previously negative (subatmospheric) pressure into the positive pressure range. Furthermore, the increase in total interstitial fluid volume rose abruptly in spite of the fact that the interstitial fluid pressure rose only slightly from that point on. Another very important effect was the character of the fluid in the interstitial spaces. The early increase in interstitial fluid volume was primarily the result of swelling in the interstitial fluid gel, but the abrupt increase in fluid that occurred when the plasma protein concentration reached its critical level for edema formation was an increase in free interstitial fluid volume while the gel fluid volume remained almost constant from this point on. The final important effect in this simulation occurred at the very end when the rate of renal loss of protein was reduced by a factor of approximately 4%. This allowed only a minute increase in protein in the plasma, but even this minute change shifted the equilibrium at the capillary membrane sufficiently to cause beginning reduction of the edema fluid and a high level of diuresis.

Once again the results from the simulation are almost identical with those that occur in patients with nephrosis, including the failure to develop sufficient amounts of edema until the protein concentration falls below a critically low level of about 1/3 normal, the critical value also found in the simulation. When tremendous amounts of fluid do collect it is almost entirely in the free fluid form, which is what the simulation shows. The simulation also shows the typical tendency for nephrotic patients to have a mild degree of circulatory collapse and slightly decreased plasma volumes. Another important feature is the changing level of urinary output, an effect that also occurs in nephrotic patients, with urinary output falling very low during those periods when large amounts of edema are being actively formed and the urinary output becoming great during those periods when edema is being resorbed. Finally, another important point of this simulation is that

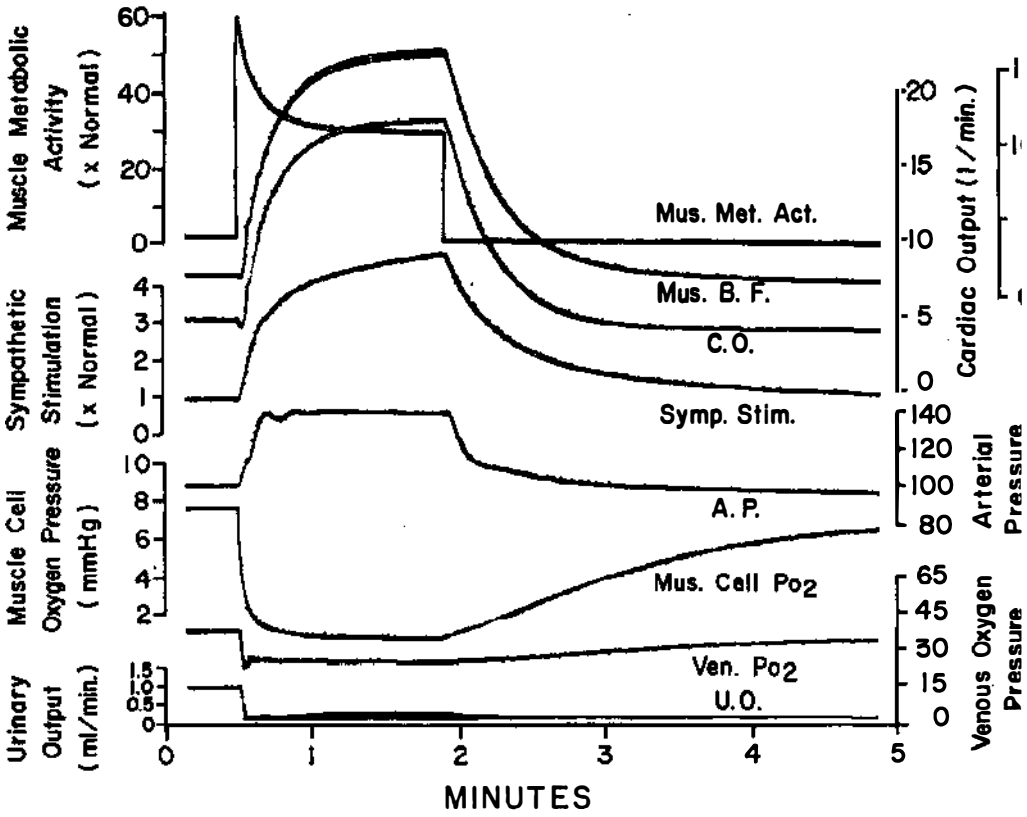

FIGURE 5. Simulation of circulatory dynamics during muscle exercise. At the initial break in the curves the muscles were activated to a level 60 times their normal value, and the degree of activation was returned to normal at the second break in the curves.

essentially all of the known circulatory effects of clinical nephrosis can be simulated without implicating any other damage to the kidneys besides simple loss of protein.

Simulation of circulatory changes during severe muscle exercise.—Figure 5 illustrates simulated changes during extremely severe exercise for a period of 1.5 minutes and for 3 minutes after the exercise was over. Displayed in the record (from top to bottom) are rate of metabolic activity in the muscles, muscle blood flow, cardiac output, degree of sympathetic stimulation, systemic arterial pressure, venous P_{O_2}, muscle intracellular P_{O_2}, and urinary output. The two initial events at the onset of the exercise were: (*a*) in-

stantaneous increase in metabolic activity of all of the muscles in the body to about sixty times their normal resting level, and (*b*) a subsequent rapid increase in the activity of the sympathetic nervous system (one-half time of about six seconds). These effects are followed within seconds by (*a*) rapid decreases in muscle cellular Po_2 and venous oxygen, and (*b*) marked increases in muscle blood flow and cardiac output. The urinary output decreased to about 0.3 ml/minute, or to the obligatory level of urinary output, and arterial pressure rose moderately during the course of the simulated exercise. Despite neurogenic driving of the muscles at the same continuous level, the metabolic activity of the muscles decreased considerably from their peak levels of activity because of development of a metabolic deficit in the muscles. When muscle exercise was abruptly stopped after 1.5 minutes, muscle metabolic activity decreased instantly essentially to normal (or perhaps even a minute amount below normal) but blood flow through the muscles continued at an elevated level for the next several minutes as did also cardiac output and arterial pressure. These effects were evidences of the metabolic deficit of the muscles and occurred during the period that the person was repaying his oxygen debt. Not shown in the curves was the effect on heart rate, which increased during extreme exercise to approximately 170 beats per minute and returned to normal along a curve similar to that for arterial blood pressure, but slightly less rapidly.

Other simulations.—Other simulations that have been performed utilizing this circulatory systems analysis include the effects of other degrees of general heart failure besides those shown in Figure 3, unilateral heart failure of the right or left side, effects of removal of the sympathetic nervous system on circulatory function, effect of infusion of different types of substances (such as saline solution, plasma, or water), effects of vasoconstrictor agents acting on different parts of the circulation, effects of extreme reduction of renal function on circulatory function, and others.

A word of caution and comment.—Despite the fact that the systems analysis of Figure 1 contains 354 blocks and more than 400 mathematical operations, and also despite the fact that the simulation is capable of predicting many if not most major circulatory changes in clinical and experimental conditions, the detailed analyses of the different sectors of circulatory function and control are based on gross functions of the parts. The analysis does not show the minute details of many of the control systems.

Three major values have come from this systems analysis. These are the following:

First, even when the details of the individual control systems of the circulation are simulated in a gross fashion, the overall results of the total systems analysis can still be highly accurate in predicting principal functions of the circulation. In other words, it does not matter from the overall point of view

whether the simulation takes into consideration all the details of the individual control systems or whether the simulation utilizes the "black box" approach to these separate controls.

Second, the systems analysis helps to identify the different control systems that are most important from a quantitative point of view in overall control of the circulation.

Third, a systems analysis such as this is very important in identifying inconsistencies between postulated mechanisms from different laboratories. To give an example, prolonged activity of very potent volume receptors operating from the heart should reduce blood volume, but blood volume actually increases in patients with congestive heart failure and very high atrial pressures. On the other hand, volume receptors that act strongly at first but adapt over a period of days would allow consistency between these two phenomena. Thus, a suggested experiment that derives from this inconsistency is to determine whether the volume receptors do indeed adapt. Many other experiments have also been suggested by similar inconsistencies found in other areas of circulatory control.

FUNCTION OF THE DIFFERENT SUBSYSTEMS FOR CIRCULATORY CONTROL

In the following pages we will attempt to use some of the principles that were forthcoming from the systems analysis of the circulatory function to build a logical pattern for circulatory control and to show how current research is adding each day to our understanding of the control mechanisms.

Control of Oxygen Delivery To Cells

We begin our discussion of the logic of circulatory control with the topic of oxygen delivery because so many of the circulatory controls seem to be geared toward this purpose. Most of the physiologic mechanisms for precise control of oxygen delivery to cells are already well known, including (*a*) changes in oxygen extraction from the blood, (*b*) changes in capillary density, (*c*) changes in vascular resistance to local blood flow, (*d*) changes in cardiac output, (*e*) changes in respiration, and (*f*) changes in circulating red blood cell mass and hematocrit.

In recent studies, both Crowell (6) and Halmagyi and co-workers (7, 8) demonstrated that oxygen transport to tissues is at least to some extent flow limited and can become seriously flow limited in hypotensive states such as hemorrhagic shock. Therefore, even a minute decrease of tissue blood flow usually causes at least some decrease of oxygen usage by the tissues. One of the most important local mechanisms to prevent decreased oxygen delivery to tissues when hypotensive states occur is the onset of vasodilatation in response to diminished local tissue oxygenation. The microelectrode studies of intracellular P_{O_2} by Whalen and co-workers (9) have been especially enlightening for several reasons. First, the time response of their measurements

is rapid enough that the records show increases and decreases in intracellular P_{O_2} occurring along with the phasic changes in capillary blood flow. These workers have shown that changing arterial P_{O_2} over very wide ranges has little effect on the intracellular P_{O_2} of many tissues, this effect being caused by increased or decreased shutdown time of capillary flow or by changes in the fraction of total blood flow passing through non-nutrient channels. These concepts are further supported by the work of Duling & Berne (10) who have shown that the P_{O_2} near the functional cells is only about 8 mm Hg instead of the 30 to 40 mm Hg usually regarded as venous P_{O_2}. Also, the P_{O_2} immediately outside the terminal ends of small arterioles was found to be about 21 mm Hg, a value less than the P_{O_2} in the veins, an effect possibly caused by "countercurrent" diffusion of oxygen from arteries to veins. Jones, Crowell & Smith (11), using an implanted capsule method, found similar values for muscle, liver, and cerebral cortex.

In the past it has been believed that the local vasodilator response to oxygen deficiency occurs in some organs but not in others. However, several different studies indicate that the vasodilatation resulting from oxygen deficiency might be a universal phenomenon throughout the systemic circulation rather than an occurrence found only in specific areas. For instance, Granger & Guyton (12) demonstrated that very significant degrees of autoregulation occur in the total systemic circulation following destruction of the central nervous system in the dog. These same effects are almost impossible to demonstrate in the dog with a normal operating nervous system because of sympathetic reflexes at work throughout the body. Although many authors in the past have felt that the liver might not autoregulate, Takeuchi and co-workers (13), studying the isolated perfused liver, have demonstrated a high degree of autoregulation in the hepatic arterial vascular system. Scholtholt & Shiraishi (14), also studying the liver, but in the intact animal, demonstrated that when the animals were artificially ventilated with a gas mixture low in oxygen, the reflex sympathetic stimulation was so great that the animal's arterial pressure rose and blood flow through the liver decreased rather than increased. Costin & Skinner (15) observed this same effect in muscle, but vasodilatation occurred when nerves to the muscle were blocked.

Most of the studies in anemia point toward at least two mechanisms by which anemia increases local blood flow. One of these is by viscosity changes (Schrier and co-workers 16) and the other is by vasodilatation resulting from reduced delivery of oxygen to the tissues (Cropp 17, Housley & Hedworth-Whitty 18). One of the principal reasons for believing that vasodilatation is a component is that breathing pure oxygen reduces the cardiac output approximately 15 percent in an anemic patient. This is approximately the amount that would be expected due to the small additional amount of oxygen dissolved in the blood. As a combined result of both of the effects that occur in anemia, Neill, Oxendine & Moore (19) have shown that the cardiac output

increases almost exactly in proportion to the degree of induced anemia in unanesthetized, trained dogs. Furthermore, these effects are unaffected by block of the sympathetic reflexes.

The vasodilatation which occurs in the hypoxic state continues to increase for long periods of time after the initial acute vasodilatation. In their studies on total systemic autoregulation, Granger & Guyton (12) found that the vasodilatation induced by decreased systemic arterial pressure continues to increase on the average for 30 minutes or more. And studies by Cassin and co-workers (20) have shown that capillary counts in relation to the total tissue mass continue to increase for many days or weeks. However, these authors believe that the prolonged increase in local blood flow occurs primarily because of opening of preexisting capillaries rather than because of increased absolute numbers of capillaries.

The systems analysis presented in the first part of this article, in general, follows the principles demonstrated by the results of animal experiments in anemia, hypoxemia, and other related states. However, there remain many unanswered questions. Among the most important of these is the relative importance of diminished oxygen in causing vasodilatation versus other metabolic factors. For instance, it is logical that carbon dioxide released from the tissue cells, because of its mass effect, could easily cause weakness of vascular smooth muscle and thereby cause dilatation. The consensus of opinion in a symposium on autoregulation and local blood flow regulation in 1963 (21) was that carbon dioxide did not have nearly so much effect in most tissues as diminished oxygen, through some workers even then felt that the carbon dioxide factor had been underrated. A recent study by Scholtholt & Shiraishi (14) has again raised this point, because increased arterial carbon dioxide in the arterial blood appears to have far more vasodilating effect on blood flow in the liver and mesenteric vessels than does hypoxia.

It is obvious that much more quantitative information is needed to determine the relative importance of the different vasodilator factors. Also there has been little progress in recent years to determine whether oxygen deficiency causes vasodilatation simply because of lack of enough oxygen for the metabolic machinery to maintain vascular contraction or whether the diminished oxygen causes release of a vasodilator substance from the tissues

Regulation of Cardiac Output

With the work of Frank and Starling at the turn of the century, a concept developed that cardiac output is regulated primarily by peripheral tissues of the body rather than by the heart itself. However, approximately a decade ago it again became fashionable to champion the idea that cardiac output is primarily controlled by the heart and nervous reflexes to the heart. Indeed, this concept still appears in the research literature (Cropp 17). However, two major events have occurred in clinical cardiology which seem to return us mainly to the original concepts of Frank and Starling. First, with the advent

of the pacemaker, it has become generally acknowledged that the heart rate can be changed in an otherwise normal heart within wide limits, and still the cardiac output remains controlled at essentially its normal value. Recent studies by Cowley (22) have shown that this is also true in the experimental animal but with an additional proviso: when the input load of venous blood is greatly increased, heart rate then becomes a very important determinant of cardiac output. The second event in clinical cardiology that has provided important conceptual information is transplantation of the heart. Carleton and co-workers (23) and Beck, Barnard & Schrire (24) have shown that even after transplantation of the human heart, the heart functions almost exactly normally even in the absence of innervation.

New measurements of ventricular function curves in normal and abnormal animals (Siegel & Downing 25, Herndon & Sagawa 26, Tsakiris et al 27, Bishop et al 28) have shown that the normal heart has far more capacity to pump higher cardiac outputs than is usually used and that the output of the heart seems normally to be determined mainly by inflow into the heart except when this inflow becomes excessively increased or except when the pumping capacity of the heart itself becomes excessively small. Thus, in heavy exercise a marked increase in heart rate (Hermansen, Ekblom & Saltin 29) and beta receptor stimulation either by the sympathetic nerves or by circulating catecholamines (29a) seem to be among the necessary factors in achieving the very large increases in required cardiac output. At the other extreme, after prolonged periods of acute hemorrhagic shock (Siegal and Downing 25) the heart loses a major share of its cardiac reserve and cardiac function then becomes one of the limiting factors in cardiac output. Likewise, following myocardial infarction (30–34) the heart becomes too weak to pump even the normal load of blood returning to it from the veins. Treatment with different agents such as hyperbaric oxygenation (30), dopamine (31), norepinephrine (32), and under some conditions acetylstrophanthidin (33) will increase the strength of the heart muscle and cause the cardiac output to return toward normal even though these same agents used in normal animals or persons rarely cause any increase in cardiac output. Also, stiffening of the ischemic myocardium occurs within a few days after an attack of myocardial ischemia (34), and this prevents aneurysmal bulging. This, too, improves the pumping capability of the heart, and the cardiac output in response returns toward normal. Thus, under failing conditions the heart seems to be the limiting factor in cardiac output regulation, while under normal conditions it is mainly peripheral factors that are limiting.

But what are the peripheral factors that are most important for regulation of cardiac output? These appear to fall into two major categories. First, the peripheral resistance and, second, the ratio of blood volume to filling capacity of the circulation (measured as mean circulatory pressure). The first of these is to a great extent controlled by the local needs of the tissues,

while the second is determined by a combination of two factors, the blood volume itself and the capacity of the vascular system. However, a very confusing factor enters into the relationship between blood volume and capacity of the circulation, namely, the phenomenon of stress relaxation. Studies on isolated blood vessels throughout the body have demonstrated high degrees of vascular relaxation following prolonged changes in pressure. And recently Prather and co-workers (35) demonstrated that the mean circulatory pressure of animals, a measure of the filling pressure of the circulation, returned to normal within two hours after massive transfusion of blood or dextran solution into dogs even though the total blood volume at that point was still 13 to 32% above normal. If these animals were bled back to normal blood volume at this point in the experiment, the animals actually showed signs of shock. These same principles could explain the results found by Coleman and co-workers (36) during the dialysis of patients for chronic renal failure, namely, a large decrease in arterial pressure and cardiac output following rapid removal of fluid from the patient but return of these factors back toward normal during the ensuing hours.

Again, the overall principles of cardiac output control which emerge from current experiments are the same as those predicted from the systems analysis of circulatory control given in this article. That is, under normal conditions output is controlled mainly by the tissues, each tissue contributing its own control of cardiac output by controlling its proportionate share of venous return. However, under abnormal conditions, such as in very heavy exercise, or in conditions that damage the heart, the heart itself then becomes the dominant factor controlling cardiac output. Note that it is the conditions in which the heart becomes the controller of cardiac output (that is, when the tissues can no longer protect their own nutritional supplies) in which death soon ensues, such as in irreversible shock and in congestive heart failure.

Regulation of Arterial Pressure Hypertension

Probably the most important contribution thus far made by the systems analysis of circulatory control has been to advance our understanding of the control of arterial pressure. The analysis demonstrates that at least three main factors play extremely important roles in pressure regulation, all of which are already known but the interrelationships of which have not been clear. These factors are (*a*) control of pressure by autonomic reflexes, (*b*) control of arterial pressure by changes in body fluid volumes and electrolytes, and (*c*) control of arterial pressure by the renin-angiotensin-aldosterone mechanism. The autonomic mechanisms will be discussed later; these seem to play their most significant role in short-term regulation of arterial pressure from second to second, minute to minute, and hour to hour, while other factors seem to play the primary role in long-term regulation of arterial pressure. However, the nervous mechanisms can affect the long-term mechanisms also, as will be pointed out.

Two devastating predictions of the systems analysis.—The systems analysis gives two extremely important predictions which were not immediately evident previously; these could change considerably the course of research in the field of blood pressure regulation and in the field of hypertension (Guyton & Coleman 2). These are the following:

1. Changes in total peripheral resistance per se play essentially no role in long-term regulation of arterial pressure.

2. It is impossible to change the arterial pressure chronically from its status quo level without either (*a*) altering the function of the kidneys in some way to change their output of water and electrolytes or (*b*) changing the intake of water and electrolytes. That is, some change in body fluid, usually as a result of a change in kidney function, must occur for chronic, long-term hypertension to develop.

These two predictions may be startling in themselves, but already there is support for them both in a large body of information which upon reflection one can readily understand. Relative to peripheral resistance, one need only to remember that opening and closing very large A-V fistulae, which can change the total peripheral resistance as much as 100%, is not associated with a measurable long-term change in arterial pressure (37). Likewise, removal of all four limbs, which increases the total peripheral resistance to as much as 160% of normal, causes no change in arterial pressure.

The second prediction, that the kidney (or changes in water and salt intake) must be involved in any long-term pressure change, derives from the fact that the kidney and mechanisms of water and salt intake operate in an integral control system as follows: As long as the arterial pressure is above normal and all other conditions of the kidney are completely normal, both the systems analysis and isolated kidney experiments show that the kidney will continue to pour out excess amounts of water and salt until the loss of this water and salt reduces the pressure back to the level at which output equals intake. Such an integral control system has infinite gain if allowed adequate time to come to equilibrium—days, weeks, months— which means that theoretically it can override all non-integrative control systems. More will be said about these predictions in subsequent paragraphs.

Role of body fluids and volumes in arterial pressure regulation.—The simulated experiment of Figure 2 illustrated the principles of arterial pressure regulation by changes in fluid volumes or filling pressure of the circulation. The main principles of this simulated experiment have been confirmed by recent experiments from the laboratories of Ledingham (3), Guyton (1, 38), Coleman (4, 5), Bianchi (39), and Ferrario (40), and they are the following: If renal function is altered to cause fluid retention, or if excess water and salt are ingested, the extracellular fluid volume begins to rise, which also increases the blood volume. This increases venous return and therefore increases cardiac output above normal. As a result, arterial pressure rises. However, the baroreceptor reflexes reduce the heart rate and cause peri-

pheral vasodilatation for the first few days to delay the rise in arterial pressure. Secondary to the increase in cardiac output, peripheral autoregulation occurs. That is, excess blood flow through the tissues increases local vascular resistance as a result of (*a*) acute local vascular constrictor effects and (*b*) long-term changes in vascular dimensions. These effects were discussed earlier in relation to local blood flow control. Once the pressure has risen to its high level, output from the kidney will have been increased to equal the intake of water and salt, and a new state of equilibrium will have been established. Note particularly that the increase in total peripheral resistance occurs as a secondary phenomenon in the elevation of arterial pressure. Also, the increase in total peripheral resistance is associated with diminished flow through all the tissues of the body, consequently returning cardiac output back toward normal. The increase in resistance is also associated with diminished capillary pressure and reduction of the body fluid volumes toward normal. Therefore, once the equilibrium state has been established, the systems analysis predicts that the cardiac output and body fluid volumes will be so near to normal in the pure fluid volume-caused hypertension that abnormalities can not be measured by usual measuring techniques. Indeed, these are the effects that have been observed by many investigators, including Julius et al (41) and Hampers et al (42).

A confusing point in the above picture has been that some types of experimental renal hypertension do not show the initial transient increase in cardiac output and fluid volumes, and some investigators have, therefore, questioned whether the basic scheme could possibly be true. However, the systems analysis predicts that if there is a simultaneous vasoconstriction in the circulation along with the tendency for water and salt retention, one could actually have decreased fluid volumes and even decreased cardiac outputs and still have hypertension caused by the tendency for water and salt retention (2), a fact that has also been confirmed by measurements in hypertensive patients with high renin activities (Tarazi, Dustan & Frohlich 43). Under these conditions the cardiac output and fluid volumes are greater than those that would have existed had it not been for the tendency for water and salt retention. A further important point is that the final level to which the arterial pressure rises is exactly the same whether or not there is a vasoconstrictor factor (Coleman and Guyton 2). On the other hand, simulating a vasoconstrictor factor in the systems analysis without the fluid retention factor causes a simulated hypertension that lasts for only a day or so, except under the following condition: If the vasoconstrictor factor is also programmed to cause vasoconstriction in the kidney, then the kidney enters into a mode tending to cause fluid retention, and hypertension ensues (2). This points up again the principle discussed earlier that fluid control must be changed from normal for chronic hypertension to be maintained.

Another important conclusion from the analysis is that return of an abnormal kidney to normal will cause return of arterial pressure to normal

in a much shorter time than required for the elevation. The reason for this is that high pressure acting on a kidney that has been returned to normal causes extremely rapid loss of water and salt, a fact illustrated by the experiments of Crawford (44) in which release of a balloon clamp on the renal artery of dogs with Goldblatt hypertension caused return of arterial pressure to normal within 24 to 36 hours, associated with very transient and minute negative fluid and salt balance. In studies by Funder et al (45), in which a renal artery clip was removed surgically from Goldblatt hypertensive sheep, the offset events in fluid balance and cardiac output were very slight when measured one day later. The minuteness of the fluid volume changes required to return blood pressure to normal in human essential hypertension during thiazide therapy has also been shown in studies by Tarazi, Dustan & Frohlich (46). Furthermore, in Goldblatt hypertension, the simultaneous vasoconstrictor effect of angiotensin can readily obscure most or all of the fluid volume and cardiac output changes (Bianchi 39) despite their theoretically overriding importance.

Both the old and the new literature (Ueda, Iwai & Yasuda 47) point out the extreme dependence of renal hypertension on salt intake. Yet, it is still questionable whether it is the salt per se or the induced volume changes resulting from this salt intake that causes the hypertension. The systems analysis suggests that it is the volume changes and not the salt, and recent studies by Brown et al (48), de la Riva et al (49), and Davidov et al (50) all support the view that sodium per se is not the factor responsible for the pressure changes. These results also fit with the earlier studies of Langston et al (51) which showed that hypertension frequently occurs in partially nephrectomized, fluid volume loaded animals despite lower than normal sodium plasma concentrations. Most investigators who have believed that sodium per se plays a significant role in the development of hypertension, have believed that the sodium causes this effect by constricting the peripheral vessels. However, the demonstration of the systems analysis that increase in total peripheral resistance without some simultaneous change in the kidney as well will cause only transient hypertension indicates that, even if sodium does cause increased arteriolar resistance in all other tissues of the body besides the kidneys, there would still be no elevated arterial pressure. However, increase in intrarenal resistance as a result of the change in sodium could indeed cause the necessary water and salt retention tendency that is required to cause chronic hypertension.

It has also often been stated that neurogenic hypertension can occur independently of fluid balance changes. However, Herd (52), recognizing the importance of the renal integrative control system for pressure control, recently pointed out that in neurogenic hypertension nervous stimuli to the kidney can cause the necessary tendency for water and salt retention. He also pointed out that this is likely to be a general phenomenon of all neurogenic types of hypertension, the initial stages of the neurogenic hypertension

being caused by the temporary hypertensive effect of increased peripheral resistance and the prolonged hypertension being caused by water and salt retention. In further support of this concept, Gill & Casper (53) have demonstrated that sympathetic stimulation causes marked retention of salt.

The final question that is raised by the systems analysis approach is whether the increase in total peripheral resistance found in most hypertensive states is a cause of the hypertension or is the result of the hypertension. Studies by Coleman et al (4, 5), by Ledingham (3), and by Conway (54) have shown that the hypertension, at least the salt loading variety, occurs first, and the increase in total peripheral resistance is a secondary phenomenon. Furthermore, the concept currently advanced is that the long-term change in total peripheral resistance results from actual vascular changes rather than simply from vasoconstriction. This has been borne out by studies of Folkow and his colleagues (55) in which they have shown that the intrinsic resistance of fully dilated tissue vascular beds increases during progressive stages of hypertension in rats that develop the condition spontaneously. Thus, it seems that a basic change in vascular dimensions and not simply a vasoconstrictor effect causes the increased total peripheral resistance in hypertensive states.

Role of the renin-angiotensin system in hypertension.—The principal question being asked today is: Does the renin-angiotensin system play significant role in most types of hypertension? Reasons for this question include the finding of Macdonald and co-workers (56) that Goldblatt hypertension occurs in rabbits equally as well after they have been immunized against angiotensin II as before, which confirms Flasher & Drury's observations (57) of more than 20 years ago that immunizing animals against renin also does not prevent typical Goldblatt nor renal-encapsulation hypertension. Furthermore, Jerums & Doyle (58) have shown that in many hypertensive patients plasma renin is lower than normal and the renin response to sodium deprivation is low. Also, measurements of renin activity in other types of hypertension, such as coarctation of the aorta (Werning et al 59 and Koletsky et al 60) and in a variety of clinical hypertensions including essential hypertension, renal parenchymal disease hypertension, and primary aldosteronism (Dustan, Tarazi & Frohlich 61) are all normal or below normal.

However, there seem to be two major exceptions to the thesis that renin plays no role in hypertension. First, Dustan and co-workers (61) found good correlation between plasma renin activity and the degree of hypertension that occurs in renovascular disease. Furthermore, large numbers of workers have in the past already pointed out the high degree of correlation between the elevated pressure and renin activities in malignant hypertension. A role that has often been suggested for renin in renal hypertension is that renin secreted by one kidney or by a damaged portion of a kidney can pass in the blood stream to the undamaged renal tissue of the same kidney or of the

opposite kidney and cause fluid and salt retention. Such a mechanism would elevate the arterial pressure, and the increased arterial pressure would perhaps make the damaged renal tissue become functional once again. Such a mechanism could play an important role in preventing uremia in patients whose renal mass is barely enough to eliminate the end-products of metabolism. With this thought in mind, Fourcade and co-workers (62) studied the possibility that minute doses of angiotensin might indeed cause water and salt retention by normal renal tissue. The studies, however, indicated that greater than physiological levels of angiotensin would be required for this mechanism to function properly under acute conditions. The study did not delineate whether or not such a mechanism could be operative under chronic conditions in which the renin could elicit aldosterone production.

Angiotensin is known to affect arterial pressure in at least several different ways, including vasoconstriction, effects on the kidneys themselves to cause water and salt retention under at least some conditions, stimulatory effect on aldosterone secretion which in turn causes water and salt retention, and enhancing autonomic effects on the circulatory system. Several studies (Fukiyama et al 63, Andersson and Eriksson 64, Scroop and Lowe 65, and Ueda et al 66) have shown, either by infusion into the vertebral arteries or into the third ventricle, that angiotensin can act directly on the brain to cause cardiovascular effects mediated by the autonomic nervous system; the main effect seems to be decreased vagal stimulation of the heart, and a lesser effect is enhancement of sympathetic activity. Fukiyama, McCubbin & Page (63) also demonstrated that the effect will continue for at least a week during continuous infusion of the angiotensin, but the maximum sustained pressure rise that can be achieved in this manner appears to be limited to only 10 to 15 mm Hg. Another effect closely associated with the autonomic effect is the ability of angiotensin to stimulate ADH release causing water retention and thereby affecting circulatory function in still another way (Mouw et al 67).

Several recent studies suggest the possibility that the renin-angiotensin system might play a more important role in acute regulation of arterial pressure than in the causation of chronic hypertension. An open-loop analysis of the renin- angiotensin system by Cowley, Miller & Guyton (68) in dogs in which the obscuring effects of nervous cardiovascular control had been removed by decapitation showed that the renin-angiotensin-vasoconstrictor system of the dog has a feedback gain of approximately 1.6. This means that a sudden decrease in arterial pressure to 50 mm Hg caused by some effect such as hemorrhage would be corrected back to approximately 80 mm Hg by operation of the renin-angiotensin-vasoconstrictor system alone, without aid from any of the other pressure regulating systems. The time for full development of this response is about 10 minutes; therefore, it could be one of the important semiacute blood pressure control mechanisms. Studies by Meyer & Worcel (69) show that administration of anti-angiotensin plasma to rats

causes very significant prompt decrease in arterial pressure, which also suggests that the vasoconstrictor effect of normally secreted angiotensin might be a continually important controller of arterial pressure. And, finally, Oparil et al (70) have demonstrated that renin activity can increase in the plasma in a matter of minutes after tilting patients on a tilt table, further supporting the view that this overall mechanism could be a valuable pressure regulator over short periods.

The mechanism of control of renin secretion is still very uncertain, although almost everyone agrees that low plasma sodium and low plasma potassium (71–75) acting directly on the kidney, enhance renin release. Blaine, Davis & Witty (76) have developed an animal preparation in which there is essentially no tubular fluid flow, and the kidneys of these animals still secrete enhanced amounts of renin in response to hyponatremia. On the other hand, Cooke et al (77) in studying renin-release induced by ethacrynic acid have shown that blockage of the ureters, with consequent blockage of tubular flow, prevents the renin release. They conclude that the stimulus for renin release after ethacrynic acid administration is change in sodium concentration in distal tubular fluid, perhaps acting at the macula densa and exerting a feedback effect on the juxta-glomerular cells. Also significant have been two other findings, that of Blair-West and his colleagues (78) that angiotensin has a direct effect on the kidneys themselves to block renin release, and that of Fojas & Schmid (79) that renin release is not greatly increased in response to decreased arterial pressure until the arterial pressure falls so low that the kidney is no longer able to autoregulate its blood flow, thus suggesting that decrease in blood flow might be much more important as a regulator of renin release than is renal intravascular pressure.

Role of aldosterone in hypertension.—The vast literature on hypertension in primary aldosteronism and on DOCA and other types of steroid-induced hypertension leave no doubt that mineralocorticoids can cause hypertension. There seems to be a tacit assumption that this type of hypertension is similar to other types of salt and water retention hypertension. However, the quantitative significance of angiotensin as a primary controller of aldosterone secretion and the mechanism by which these hormones act together in hypertension still remain highly problematical. Several different studies have indicated that Goldblatt hypertension and other renal types of hypertension do not depend on this mechanism. For example, a demonstration by Blair-West and his colleagues (80) shows that Goldblatt hypertension occurs equally well in steroid supported animals whose adrenal glands have been removed as in normal animals, a fact that supports the earlier study of McCaa et al (81) that adrenal secretion of aldosterone can actually be markedly decreased in Goldblatt hypertension rather than increased. These facts also fit with the observation of Bull et al (82) that it is mainly sodium concentration in the body fluids that controls the renin aldosterone system,

rather than blood volume or pressure, indicating that the primary function of aldosterone is to control sodium.

The quantitative importance of the different factors that control aldosterone secretion rate is still confusing: many investigators support angiotensin control as the major factor while others support central control by the nervous system and neurohormones. Though little headway has been made in this controversy, a study by Horton (83) has shown that injection of small amounts of adrenocorticotropic hormone is a stronger stimulus in man for the production of aldosterone than is an infusion of angiotensin in amounts that cause hypertension.

Control of Body Fluid Volumes

One of the important features of the systems analysis presented earlier is the intricate interplay of many factors required for control of body fluid volumes, not merely the concepts of volume receptors, hemodynamic factors, or renal output of fluid taken individually but, rather, the combination of all these factors and still many others. But, first, let us see what has been done recently and then return to the systems analysis.

Antidiuresis, thirst, and salt appetite.—Additional studies confirm that increased atrial transmural pressure elicits a reflex to cause increased water and salt output by the kidneys (84, 85). Johnson, Zehr & Moore (84) also found simultaneous decrease in ADH secretion, but Goetz et al (85) found no change in ADH.

The regulation of thirst and intake of water is closely associated with the regulation of antidiuretic activity, and essentially the same factors affect both of these mechanisms. Stricker's studies (86, 87), for instance, show that both a decrease in plasma volume and an increase in osmolality, the same factors that affect antidiuretic hormone secretion, likewise stimulate thirst. Thus, the two mechanisms complement each other.

Still another factor important to circulatory homeostasis is the appetite for salt. Stricker & Jalowiec's (87) studies point out that osmotic dilution stimulates the salt appetite in rats and that this is probably equally as important a mechanism for repletion of body fluid volumes as are the thirst and antidiuretic mechanisms.

Natriuresis.—The old observation is that extracellular fluid volume expansion, caused in a number of different ways, but particularly by saline infusion, is associated with marked natriuresis. This effect occurs without any plasma expansion (Reyburn & Gilmore 88) but it is highly correlated with the increase in the interstitial fluid volume increase (Higgins 89). Also, the effect is promoted more by changes in sodium load than by changes in volume load per se (Schrier et al 90). Finally, studies of Higgins (91), Stumpe, Lowitz & Ochwadt (92), and Bank et al (93) all demonstrate that there is

decreased proximal tubular sodium reabsorption; it is also suggested that this effect might be caused by physical factors in the kidney, especially by increased renal interstitial fluid volume which diminishes the sizes of the tubules and their absorptive capability. Schrier and co-workers (16) have implicated still other physical factors, including decreased blood viscosity and decreased colloid content of the plasma, which can affect pressures and osmotic absorption at different points in the kidneys including in the glomeruli, the peritubular capillaries, and the vasa recta. Schultze, Shapiro & Bricker (94) point out that the phenomenon of increased single nephron natriuresis that occurs when only a few viable nephrons remain exhibits nearly the same effects as those which occur in the saline diuresis phenomenon, and they conclude that the two phenomena might be, at least partially, manifestations of the same mechanism.

Whether or not a natriuretic factor (third factor) actually exists to cause natriuresis following saline loading is still a matter of discussion. Bonjour & Peters (95) were unable to find such a natriuretic factor in cross-circulation experiments. On the other hand, Sealey, Kirshman & Laragh (96) do report a weakly natriuretic factor that is slow to act, that can have an effect for as long as three hours after injection, but that acts only under special conditions. Thus, the significance of the natriuretic factor is still much in doubt.

Renal autoregulation.—At least two studies (92, 97) have pointed out that autoregulation of arterial pressure and of glomerular filtration rate does not prevent tremendous increases in urine output when the arterial pressure increases, an increase in urine output from 6 to 20 fold occurring when the arterial pressure rises from 100 to 200 mm Hg. In animals with diabetes insipidus (Navar, Uther & Baer 97), enough increase in glomerular filtration rate was observed to account for the increase in water loss. On the other hand, the studies of Stumpe, Lowitz & Ochwadt (92) indicated instead that the marked increase in the urine flow rate is caused by decreased sodium and water reabsorption along the loop of Henle. However, in overall circulatory regulation, the important point is simply that increased arterial pressure does indeed cause marked increases in both water and salt output despite autoregulation in the kidney.

The possibility that feedback at the macula densa is the cause of renal autoregulation also still receives attention. Most important has been the observation by Schnermann et al (98) that perfusion of the loop of Henle with Ringer's solution at different rates of flow causes changes in afferent arteriolar resistance, presumably mediated by the juxtaglomerular apparatus. On the other hand, Gagnon and co-workers (99) have shown that maneuvers to block the action of angiotensin on the afferent arteriole do not prevent renal autoregulation, thus indicating that the earlier suggestion of Thurau (100) that feedback at the juxtaglomerular apparatus is effected through intermediation of renin and angiotensin probably is not correct. Therefore, some other type of feedback stimulus might still need to be found.

Role of hemodynamic factors in volume regulation.—Most of the hemodynamic factors that affect renal output of urine are well known and are not the subject of much research. These factors include increase in renal arterial pressure, changes in renal resistances caused by nervous factors, changes in plasma colloid osmotic pressure and changes in blood viscosity. The systems analysis presented in this article demonstrates particularly that blood viscosity and plasma colloid osmotic pressure could play far greater roles in control of urinary output than have previously been believed. Studies by Schrier et al (16) support both of these observations, and Spitzer & Windhager (101) have shown that increased colloid osmotic pressure can not only decrease glomerular filtration rate but can also increase reabsorption of water and salt from the proximal tubules as well. Furthermore, because of the very fine balance that exists between glomerular filtration rate and tubular absorption, even minute changes in either of these can cause tremendous changes in urine output. This could explain the extreme sensitivity of diuretic and natriuretic responses to renal hemodynamic factors and to volume expansion or saline loading.

Regulation of interstitial fluid volume.—The systems analysis also explains how the interstitial fluid volume can be regulated very precisely. This subject is reviewed in detail elsewhere by Guyton, Granger & Taylor (102), but the gist of it is the following: The interstitial fluid exists in two phases, as free fluid and as fluid imbibed in a gel-like ground substance. Under normal conditions, essentially all of this fluid is in the latter form, with only minute portions of free fluid. When free fluid increases even slightly, lymphatic flow also increases tremendously (Taylor et al 103) thereby acting normally as a negative feedback mechanism to prevent any significant increase in free fluid in the tissue spaces. Lymph flow removes protein as well as water from the tissue spaces, decreasing tissue colloid osmotic pressure and increasing capillary absorption of fluid. On the other hand, the interstitial fluid gel, because of its imbibition properties, pulls fluid into it from the free fluid phase. The amount of fluid held in the gel is determined primarily by its imbibition forces, and the quantity of this fluid is relatively stable—at least this is so for short-term hemodynamic function. In brief, the lymphatic system (and capillary absorption) normally seem to keep the interstitial fluid spaces relatively "dry" of free interstitial fluid. Therefore, the normal volume of interstitial fluid volume is almost entirely that volume imbibed in the tissue gel. When the normal drying mechanism for the interstitial spaces fails to maintain the dry state, then large quantities of free fluid begin to collect, and edema ensues.

Reflex Control of the Circulation

Reflex control of the circulation takes last place in this discussion not because it is unimportant but because most of the current research work is mainly confirmation of previous studies or is the study of patterns of cardio-

vascular responses following (*a*) vagal afferent stimulation (Oberg & White 104), (*b*) stimulation of the baroreceptor system in man (Beiser et al 105 and Epstein et al 106), and (*c*) chemoreceptor stimulation (Kontos, Vetrovec & Richardson 107).

Several quantitative studies have been performed to determine the overall effectiveness of the baroreceptor system and its mode of action. Allison, Sagawa & Kumada (108) performed an open-loop analysis of the aortic arch barostatic reflex and found that it functions very much the same as the carotid sinus reflex, except that higher arterial pressures are required to excite the system. Hainsworth, Ledsome & Carswell (109) have also studied baroreceptor responses from the aortic arch and compared these with carotid sinus responses. The responses are qualitatively the same, and the experiments indicate that signals from the aortic stretch receptors and from the carotid stretch receptors sum to produce the same types of effects.

Kumada & Sagawa (110) demonstrated that blood volume changes of 10 to 20% cause a 21 to 31% change in impulse traffic in the aortic nerves of the rabbit, this occurring with only a 6% increase in arterial pressure. Therefore they suggest that arterial baroreceptors act as "volume" receptors in the same way as do atrial receptors. However, the study also demonstrates that so-called "volume" receptors cannot be distinguished from pressure receptors.

In view of the great emphasis that has been placed on pulse pressure as a stimulus to the baroreceptors in recent years, perhaps one of the most important recent papers is that of Kumada et al (111) demonstrating that the pulsatile component of the carotid sinus reflex does not improve the reflex response of an animal to hemorrhage. This experiment was performed by preventing the pulses from reaching the carotid sinus area.

A new study has confirmed the concept of resetting of the baroreceptors. Krieger (112) demonstrated that essentially all baroreceptors are reset within 24 to 48 hours in the rat. This study, added to previous studies on resetting of vascular stretch reflexes, indicates that these reflexes exert their effects only during the first few hours to the first few days after pressure changes occur, and that other mechanisms are required for long-term regulation—either chemoreceptors reflexes or the intrinsic controls of the circulatory system itself. Another type of resetting was demonstrated by Alexander & De Cuir (113), who showed that the heart rate in the rabbit, after rising markedly immediately following sinoaortic denervation, returned to normal within two to six days when only one side was denervated and returned 50% toward normal within two to five weeks when both sides were denervated.

CONCLUDING REMARKS

Again it should be repeated that this attempt to combine a systems analysis with a review was a purposeful experiment. A disadvantage has been

that a systems analysis in itself requires a tremendous amount of space for explanation, and even then the origins of the different components must unfortunately be omitted, or alternatively they would require an entire book to explain. However, those of us who have made this systems analysis will testify that such a procedure forces one into a pattern of logical thinking and logical organization, whether the results in all instances are correct or not. If the general principles of this systems analysis are correct, and we believe they are, then it seems clear that the field of circulatory physiology is on the verge of changing from the realm of a speculative science to that of an engineering science.

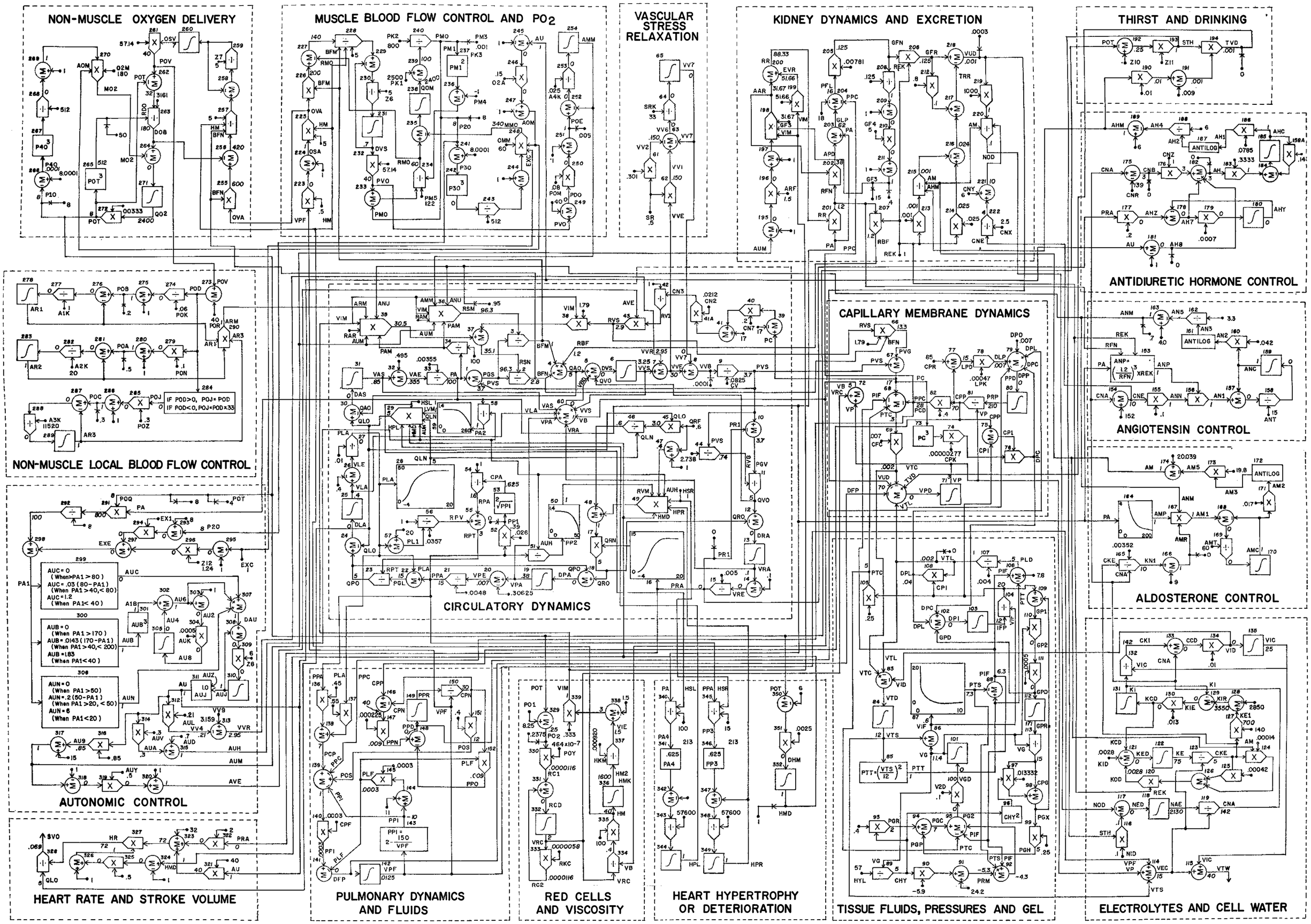

FIGURE 1. Systems analysis diagram for regulation of the circulation. Units are the following: volume in liters; mass in grams; time in minutes; chemical units in milliequivalents; pressure in millimeters of mercury; control factors in arbitrary units but in most instances expressed as the ratio to normal—for instance, a value of 1 represents normal. Normal values are given on the lines that represent the respective variables.

The following is a list of the important dependent and independent variables in the analysis (additional variables are present for purposes of calculation but generally have no physiological significance):

AAR—afferent arteriolar resistance
AHM—antidiuretic hormone multiplier, ratio of normal effect
AM—aldosterone multiplier, ratio of normal effect
AMC—aldosterone concentration
AMM—muscle vascular constriction caused by local tissue control, ratio to resting state
AMP—effect of arterial pressure on rate of aldosterone secretion
AMR—effect of sodium to potassium ratio on aldosterone secretion rate
AMT—time constant of aldosterone accumulation and destruction
ANC—angiotensin concentration
ANM—angiotensin multiplier effect on vascular resistance, ratio to normal
ANN—effect of sodium concentration on rate of angiotensin formation
ANP—effect of renal blood flow on angiotensin formation
ANT—time constant of angiotensin accumulation and destruction
ANU—nonrenal effect of angiotensin
AOM—autonomic effect on tissue oxygen utilization
APD—afferent arteriolar pressure drop
ARF—intensity of sympathetic effects on renal function
ARM—vasoconstrictor effect of all types of autoregulation
AR1—vasoconstrictor effect of rapid autoregulation
AR2—vasoconstrictor effects of intermediate autoregulation
AR3—vasoconstrictor effect of long-term autoregulation
AU—overall activity of autonomic system, ratio to normal
AUB—effect of baroreceptors on autoregulation
AUC—effect of chemoreceptors on autonomic stimulation
AUH—autonomic stimulation of heart, ratio to normal
AUK—time constant of baroreceptor adaptation
AUL—sensitivity of sympathetic control of vascular capacitance
AUM—sympathetic vasoconstrictor effect on arteries
AUN—effect of CNS ischemic reflex on autoregulation
AUV—sensitivity control of autonomics on heart function
AUY—sensitivity of sympathetic control of veins
AUZ—overall sensitivity of autonomic control
AVE—sympathetic vasoconstrictor effect on veins
A1K—time constant of rapid autoregulation
A2K—time constant of intermediate autoregulation
A3K—time constant of long-term autoregulation
A4K—time constant for muscle local vascular response to metabolic activity
BFM—muscle blood flow
BFN—blood flow in non-muscle, non-renal tissues
CA—capacitance of systemic arteries
CCD—concentration gradient across cell membrane
CHY—concentration of hyaluronic acid in tissue fluids
CKE—extracellular potassium concentration
CKI—intracellular potassium concentration
CNA—extracellular sodium concentration
CNE—sodium concentration abnormality causing third factor effect
CPG—concentration of protein in tissue gel
CPI—concentration of protein in free interstitial fluid
CPN—concentration of protein in pulmonary fluids
CPP—plasma protein concentration
CV—venous capacitance
DAS—rate of volume increase of systemic arteries
DPF—rate of increase in pulmonary free fluid
DHM—rate of cardiac deterioration caused by hypoxia
DLA—rate of volume increase in pulmonary veins and left atrium
DLP—rate of formation of plasma protein by liver
DOB—rate of oxygen delivery to non-muscle cells
DPA—rate of increase in pulmonary volume
DPC—rate of loss of plasma proteins through systemic capillaries
DPI—rate of change of protein in free interstitial fluid
DPL—rate of systemic lymphatic return of protein
DPO—rate of loss of plasma protein
DRA—rate of increase in right atrial volume
DVS—rate of increase in venous vascular volume
EVR—postglomerular resistance
EXC—exercise activity, ratio to activity at rest
EXE—exercise effect on autonomic stimulation
GFN—glomerular filtration rate of undamaged kidney
GFR—glomerular filtration rate
GLP—glomerular pressure
GPD—rate of increase of protein in gel
GPR—total protein in gel
HM—hematocrit
HMD—cardiac depressant effect of hypoxia
HPL—hypertrophy effect on left ventricle
HPR—hypertrophy effect on heart, ratio to normal
HR—heart rate
HSL—basic left ventricular strength
HSR—basic strength of right ventricle
HYL—quantity of hyaluronic acid in tissues
IFP—interstitial fluid protein
KCD—ra.e of change of potassium concentration
KE—total extracellular fluid potassium
KED—rate of change of extracellular fluid concentration
KI—total intracellular potassium concentration
KID—rate of potassium intake
KOD—rate of renal loss of potassium
LVM—effect of aortic pressure on left ventricular output
MMO—rate of oxygen utilization by muscle cells
MO2—rate of oxygen utilization by non-muscle cells
NAE—total extracellular sodium
NED—rate of change of sodium in intracellular fluids
NID—rate of sodium intake
NOD—rate of renal excretion of sodium
OMM—muscle oxygen utilization at rest
OSA—aortic oxygen saturation
OSV—non-muscle venous oxygen saturation
OVA—oxygen volume in aortic blood
OVS—muscle venous oxygen saturation
O2M—basic oxygen utilization in non-muscle body tissues
PA—aortic pressure
PAM—effect of arterial pressure in distending arteries, ratio to normal
PC—capillary pressure
PCD—net pressure gradient across capillary membrane
PCP—pulmonary capillary pressure
PDO—difference between muscle venous oxygen P_{O_2} and normal venous oxygen P_{O_2}
PFI—rate of transfer of fluid across pulmonary capillaries
PFL—renal filtration pressure
PGC—colloid osmotic pressure of tissue gel
PGH—absorbency effect of gel caused by recoil of gel reticulum
PGL—pressure gradient in lungs
PGP—colloid osmotic pressure of tissue gel caused by entrapped protein
PGR—colloid osmotic pressure of interstitial gel caused by Donnan equilibrium
PIF—interstitial fluid pressure
PLA—left atrial pressure
PLD—pressure gradient to cause lymphatic flow
PLF—pulmonary lymphatic flow
PMO—muscle cell P_{O_2}
POD—non-muscle venous P_{O_2} minus normal value
POK—sensitivity of rapid system of autoregulation
PON—sensitivity of intermediate autoregulation
POS—pulmonary interstitial fluid colloid osmotic pressure
POT—non-muscle cell P_{O_2}
POV—non-muscle venous P_{O_2}
POY—sensitivity of red cell production
PO2—sensitivity of long-term autoregulation
PO2—oxygen deficit factor causing red cell production
PPA—pulmonary arterial pressure
PPC—plasma colloid osmotic pressure
PPD—rate of change of protein in pulmonary fluids
PPI—pulmonary interstitial fluid pressure
PPN—rate of pulmonary capillary protein loss
PPO—pulmonary lymph protein flow
PPR—total protein in pulmonary fluids
PRA—right atrial pressure
PRM—pressure caused by compression of interstitial fluid gel reticulum
PRP—total plasma protein
PTC—interstitial fluid colloid osmotic pressure
PTS—solid tissue pressure
PTT—total tissue pressure
PGV—pressure from veins to right atrium
PVG—venous pressure gradient
PVO—muscle venous P_{O_2}
PVS—average venous pressure
QAO—blood flow in the systemic arterial system
QLN—basic left ventricular output
QLO—output of left ventricle
QOM—total volume of oxygen in muscle cells
QO2—non-muscle total cellular oxygen
QPO—rate of blood flow into pulmonary veins and left atrium
QRF—feedback effect of left ventricular function on right ventricular function
QRN—basic right ventricular output
QRO—actual right ventricular output
QVO—rate of blood flow from veins into right atrium
RAM—basic vascular resistance of muscles
RAR—basic resistance of non-muscular and non-renal arteries
RBF—renal blood flow
RCI—red cell production rate
RC2—red cell destruction rate
RCD—rate of change of red cell mass
REK—percent of normal renal function
RFN—renal blood flow if kidney is not damaged
RKC—rate factor for red cell destruction
RMO—rate of oxygen transport to muscle cells
RPA—pulmonary arterial resistance
RPT—pulmonary vascular resistance
RPV—pulmonary venous resistance
RR—renal resistance
RSM—vascular resistance in muscles
RSN—vascular resistance in non-muscle, non-renal tissues
RVG—resistance from veins to right atrium
RVM—depressing effect on right ventricle of pulmonary arterial pressure
RVS—venous resistance
SR—intensity factor for stress relaxation
SRK—time constant for stress relaxation
STH—effect of tissue hypoxia on salt and water intake
SVO—stroke volume output
TRR—tubular reabsorption rate
TVD—rate of drinking
VAS—volume in systemic arteries
VB—blood volume
VEC—extracellular fluid volume
VG—volume of interstitial fluid gel
VGD—rate of change of tissue gel volumes
VIB—blood viscosity, ratio to that of water
VIC—cell volume
VID—rate of fluid transfer between interstitial fluid and cells
VIE—portion of blood viscosity caused by red blood cells
VIF—volume of free interstitial fluid
VIM—blood viscosity (ratio to normal blood)
VLA—volume in left atrium
VP—plasma volume
VPA—volume in pulmonary arteries
VPD—rate of change of plasma volume
VPF—pulmonary free fluid volume
VRA—right atrial volume
VRC—volume of red blood cells
VTC—rate of fluid transfer across systemic capillary membranes
VTD—rate of volume change in total interstitial fluid
VTL—rate of systemic lymph flow
VTS—total interstitial fluid volume
VTW—total body water
VUD—rate of urinary output
VV7—increased vascular volume caused by stress relaxation
VVR—diminished vascular volume caused by sympathetic stimulation
VVS—venous vascular volume
Z8—time constant of autonomic response

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