In spite of the fact that much is known regarding various factors which determine blood pressure, the mechanism(s) responsible for hypertension remain elusive. The mystery applies not only to essential hypertension, but also to renal and, indeed, even to the hypertension associated with coarctation, adrenal tumors, and elevated intracranial pressure. Almost characteristically, investigators who have discovered promising clues have become frustrated in their efforts to apply these clues to the “intact” hypertensive. These clues seem to become swallowed up and lost in the many interacting functions related to blood-pressure control. This discussion constitutes an attempt to consider why many clues to the etiology of hypertension appear promising when considered alone but do not seem to explain the abnormality when sought in the hypertensive patient or experimental animal.

Investigators and clinicians alike have tended to divide the body into traditional systems, such as gastrointestinal, cardiovascular, endocrine, etc. Such conventional segregation may, however, become inappropriate for investigative purposes since few physiological functions themselves follow such traditions. Furthermore, investigators have found it difficult to consider more than one function at a time. The usual biomedical experiment consists of measuring one, or at most very few, independent and dependent variables with the hopeful assumption that other related variables are in a “steady state.” It has, of course, long been recognized that such experiments are not ideal, but may be necessitated by methodological difficulties and by the nature of experimental subjects.

While the biomedical investigator’s task is not easy, it is nevertheless essential that he learn to deal with multiple simultaneous variables and their functional interactions. Conversely, he will be misled and nature’s mechanism will elude him if he cannot consider complex systems, since such are nature’s mechanisms. It is possible to select many examples of biological systems to illustrate the fact that, in such systems, the relationships between any two variables are dependent upon the simultaneous state of other variables. Thus, if an investigator is interested in determining the relationship between two variables, he will be misled if the variables are also affected by other functions of which he is unaware or which he does not measure simultaneously.

An example of this “fact of life,” is the familiar and relatively simple feed-back loop, as illustrated in figure 1(a). Here (Y) represents some significant input into the system and (0) is the related significant output. (A) represents the properties and behavior or function of the box containing A. For example, this might be an electrical system, such as an amplifier, where the input and output are electrical voltage and where (A) is the gain. (A) could also represent a biological function which is in the feed-back loop, so that the output from the A “box” is fed through the B “box” and the output from B is then fed back into the input of A. This is a common engineering technique, and, as will be reiterated, is also a common occurrence in biological systems. In the illustration, (X) is the difference between the input (Y) and the output of B which is BAX.* X is sometimes called the “error,” if this represents a regulatory system.

*When BAX is negative with respect to Y, i.e., negative feed-back.
The usual practice in ascertaining the properties and characteristics or functions of a system is to relate the output to the input. Again, this is true, not only of engineering practice, but also in science including biomedical science. The function relating the input and output is often called the transfer function. For example in the equation:

\[ Y = \frac{A}{1 + AB} \]  

Thus, \( A/(1 + AB) \) is the transfer function of the system.

It is important to note that changes in either \( A \) or \( B \) will affect the output \( O \) for a given input \( Y \). For example, if the function \( A \) may remain constant, while only a slight change in \( B \) may affect the output of the system. Unless the investigator either measured simultaneously the input-output of both \( B \) and \( A \), or unless he knew the function \( B \) at the same time that he measured the input-output relationship of \( A \), he might think \( A \) had changed, and moreover, he would not be able to ascertain \( A \). It should be noted that when \( AB \) approaches \(-1\), then \( O/Y \) approaches infinity. It is important to note that feedback can also suppress changes which might otherwise tend to occur in the output when the function of \( A \) became altered.

If the system gained one additional degree of complexity, as represented in figure 1(b), then the transfer function becomes considerably more complex. Also, it is important to consider the type of functions which \( A \) and \( B \) may represent and how such functions will affect the kinds of measurements which must be made in order to characterize the system. Of course, \( A \) and \( B \) could be anything from functions which could be represented by simple algebraic terms, multiplication, division, addition or subtraction, to functions which range from linear to nonlinear differential equations. It is becoming increasingly evident that many biological functions are so complex that they can be represented only by differential equations. If they are linear, then mathematical techniques (transforms) permit them to be handled as algebraic functions. If they are nonlinear, as many probably are, then the handling of such systems may become formidable.

An example of a familiar and relatively simple linear, second-order differential equation is:

\[ F(t) = EX + R \frac{dx}{dt} + M \frac{d^2x}{dt^2} \]

which is the equation of motion in a one-dimensional system. Thus, \( F(t) \) is the force applied to a simple system, \( X \) represents the lineal one-dimensional displacement, \( \frac{dx}{dt} \) the velocity of the displaced material, and \( \frac{d^2x}{dt^2} \) the acceleration. Thus, if the system contains elasticity, viscosity, and inertia or mass which affect the system's motion, then these properties can only be assessed by simultaneously and instantaneously measuring the applied force, the displacement, velocity, and acceleration. Conversely, if only the displacement were measured together with the force, one would not be able to characterize...
the system nor predict its behavior for a different force. Again, to relate this to biology, it is a fact that if the biological function is such that the output is not only a function of how much the input varies, but also how rapidly it varies, then the input variability must be measured with respect to time as well as with respect only to the magnitude of the variability, if the system is to be characterized.

Now that two relatively simple kinds of functional relationships among variables have been exemplified, it may be germane to reconsider the matter of blood pressure control. Figure 2 represents an admittedly over-simplified diagram of some of the major functions which investigators have linked in the control of blood pressure. Even in such a simplified schema, the multiple feed-back nature is evident.

Consideration of this array may begin with the blood vessel since, regardless of the etiological mechanism(s) of hypertension, the final common path is the blood vessel wall. It is generally agreed that the resistance to blood flow is increased and that this increase is due to alterations in the properties of the vascular walls. These properties are those which determine the radius that the vessel assumes with respect to the prevailing distending pressure, i.e., the difference between the blood pressure and the pressure surrounding the vessel. On the arterial side, of course, the distending pressure is predominantly the blood pressure and these properties are often collectively referred to as vascular tone. These properties are labeled as mechanical because they relate to mechanical forces and energy in contrast to electrical, thermal, and chemical properties.

These mechanical properties which determine the tone and set the radius of the vessel for a given distending pressure have been analyzed and discussed in detail elsewhere. Changes in these properties have effects on the system we are considering in addition to the effect on so-called peripheral resistance, and these other effects may be used as a starting point of this consideration of the system illustrated in figure 2. It is not only instructive but also sobering, as one peruses this array, to note how little we know in a quantitative way about each “black box.”

Proceeding vertically upward from the blood vessel in figure 2, it is noted that changes in mechanical properties of the vessel walls which contain the so-called pressure and volume receptors will alter the response of these receptors to the prevailing vessel distention. These various receptors have been lumped into the common and appropriate term mechanoreceptor, since they probably all respond to mechanical force and are probably all stretch receptors or, more properly, strain receptors. Since they are located in the walls of blood vessels, the extent that they are stretched depends upon the distending pressure and upon the stiffness or tone of the containing vessel walls. The electrical activity of these receptors, which constitutes the information they transmit to the central nervous system from the vascular system, therefore, depends upon (a) the vascular distending pressure, (b) the stiffness or tone of the vessel walls, i.e., their mechanical properties, and (c) the properties of the receptors themselves and the manner in which they are coupled to the vessel wall. The properties of the wall and of the receptors are such that the rate of change of pressure is important as well as the pressure itself.

The information input from these receptors into the central nervous system is then integrated and processed by the central nervous system, together with inputs from many other sources and, indeed, as a function of the properties and behavior of the central nervous system, which is also a function of the properties of the blood vessel walls, i.e., in determining cerebral blood flow.

One of the major outputs of the central nervous system is the efferent autonomic nervous outflow constituted chiefly by the sympathetic nervous system responsible for the so-called sympathetic vasomotor tone. This is mediated by the effector catecholamines lib-
erated by the sympathetic nerve endings associated with the vascular smooth muscle.

The properties and behavior of vascular smooth muscle then affect the tension within the wall of the blood vessel. The stiffness of the wall of the vessel thus influences the tone of the wall, the vessel radius, and consequently affects the blood pressure. These changes then affect, in a feedback manner, the mechanoreceptor activity if the walls of the vessels containing receptors are affected by vasomotor influences. These changes also "feed back" to the muscle, since its properties are functions of its length and tension.

We may now consider another loop prevalent in current hypertension research, i.e., the renal-adrenal cortex loop. Here again the loop begins with the blood vessel, since the renal circulation is considered to be the stimulus to the formation of renin, presumably from the juxtaglomerular cells. The angiotensin resulting from the action of renin on substrate then is considered to stimulate the adrenal cortex to release aldosterone. The aldosterone then affects the electrolyte and water handling by the renal tubules. The retention of sodium and water affected by aldosterone then may cause alterations of the vessel wall, thus also changing their mechanical properties. Of course, this loop may be further complicated by direct actions of angiotensin upon the vascular smooth muscles and by the effects of altered vessel wall electrolyte concentrations on smooth muscle contractility. It is also seen that there may be other influences of the adrenal cortex in addition to those of the renal-endocrine mechanism, e.g., the adrenal cortical hormones affect the contractile properties of smooth muscle.

One of the difficulties in explaining the altered vessel water and electrolyte content in hypertension by the renal-aldosterone loop is that it does not satisfactorily explain why alterations in electrolyte concentrations occur when, as is frequently observed, their concent...
trations in the fluid which surrounds the ves-

sion wall, as reflected by the plasma concentra-
tions, are apparently normal. This suggests
the existence of some mechanism(s) for con-
centrating sodium and perhaps other ions
in the vessel walls. These "other" mechan-
ism(s), referred to in figure 2, are very
poorly understood, and one has either great
liberty, or no liberty at all, in speculating on
the existence of other loops relating again,
the blood vessel walls which affect the circu-
lation in the vessel walls, in endocrine glands,
in the central nervous system or, indeed, in
almost any tissue of the body.

Another area of great ignorance is por-
trayed by the box labeled "efferent effects,"
relating the central nervous system, the ad-
renal cortex and "other" mechanisms. While
these pathways are not understood, there is
certainly evidence that such pathways do
exist. Also, there is the adrenal medulla which
may affect the mechanical properties of the
vascular walls by the release of vasoactive
amines acting directly on smooth muscle and/
or by altering the metabolism of the tissues
of the vessel wall.

As stated, it is sobering to consider even
this admittedly overly-simplified picture of
factors which control blood pressure. Even
in its relative simplicity, it is evident that
many feed-back loops exist and that each one
of the boxes represents transfer functions
which would be represented by equations of
varying degrees of complexity; they may be
represented by differential equations in many
cases and often by series of simultaneous dif-
ferential equations.

It is also evident that the effects of altera-
tions of any one of the boxes, or relationships
between boxes, will depend upon the simul-
taneous state of all other boxes and their
inter-relationships. It is not surprising, then,
that the "frustration index" of research in
hypertension is very high and it may explain
why so many seemingly valuable clues to the
etiology of hypertension become obscured in
the intact hypertensive subject.

It is perhaps incumbent upon anyone who
emphasizes the difficulties in dealing with
such a complex problem to offer some sugges-
tions as to how these difficulties can be alle-
viated, or at least attenuated. We can, I
believe, be encouraged by the fact that tech-
niques are rapidly being developed which
permit investigators to begin to handle multi-
variable systems. Such complexity is not
unique to biologists, although biological sys-
tems seem to be as complex as any in nature.
Interestingly enough, engineers, militarists,
management scientists, and natural
scientists, such as astronomers, have pioneered
the advancements in analytical techniques and
computer technology which are necessary to
handle the multiple, complex variables charac-
teristic of so much of the world and its
surroundings.

More than analytical techniques and com-
puters are, however, required to investigate
and understand the properties and behavior
of systems. There must also be a certain pre-
requisite understanding of the properties and
behavior of the system to which the analytical
techniques can be applied for computer pro-
graming. Thus, it is a progressive, iterative
process and, in hypertension research, it is
evident that we are in the initial stages of
this process. It is necessary to begin by con-
structing as characteristic a picture of the
system as possible and to attempt to char-
acterize as many of the boxes as possible with
regard to their transfer functions and inter-
actions. In the space and time allotted herein,
it is not possible to consider each of the
"black boxes." Indeed, to assemble all avail-
able information and to attempt to formulate
transfer functions is a formidable task. Fur-
thermore, it is certain that available infor-
mation is still too meager and descriptive to
permit derivations of transfer functions of
most boxes. This represents the future task
of many investigators and much time. My
purpose here is only to select some examples
to illustrate the kind of task we face as in-
vestigators of disease processes.

We might begin again with the mechanical
properties of the blood vessels. Figure 3 rep-
FIGURE 3

The right-hand figure represents a thick-walled vessel, and the left-hand figure, a thin-walled vessel. See text for definitions of symbols.

The left-hand figure represents a "thin-walled" vessel where \( \delta \) is the wall thickness which is small compared to the radius \( r \), i.e., external and internal radii are not significantly different. In this case, the relationship between \( T \) and \( P \) can be written:

\[
T = P \left( \frac{\delta}{\delta} \right) . \tag{7}
\]

Next, it is necessary to establish the relationship between tension within the wall and the resulting wall strain, \( \epsilon \). These relationships establish the mechanical properties of the wall itself, i.e., the elastic, viscous, and inertial properties which determine how much the wall will stretch for a given tension and rate of application. These considerations have been discussed in detail elsewhere. \(^5\) In summary, the mechanical properties of the large arteries have been investigated, i.e., those which correspond to thin-walled vessels. These investigations have been limited to the aorta and its major branches. Equations permitting transfer functions for these vessels have been written. \(^4\)

\[
P \left( \frac{\delta}{\delta} \right) = E \epsilon + R \frac{d \epsilon}{dt}, \tag{8}
\]

where \( E \) and \( R \) represent the lumped elastic and viscous coefficients of the vessel wall.

It is evident that much work remains before similar functions can be written for the smaller vessels of the arterial tree, since the thin-walled approximations cannot be applied and it is much more difficult to make reliable stress-strain measurements on small vessels in vivo.

When we consider the factors which determine the vascular tone and its variability, it is again evident that knowledge is still inadequate to describe their transfer functions. Figure 2 contains two boxes which represent functions known to affect vessel wall properties and are thought to be important in the etiology of hypertension. The paucity of information on vascular smooth muscle became strikingly evident during a recent symposium on this subject. \(^4\) Most knowledge of muscle properties and behavior relates to striated muscle, and its similarity or lack thereof to smooth muscle is not yet understood. It is clear, however, that the chemical environment of vascular smooth muscle is important in determining its properties. It is also evident that the tension applied to the muscle is important in determining its properties.

The dependence of muscle behavior on its chemical and mechanical environment establishes several feedback loops which interact with each other. One of the chemical loops relates to the box labeled \( H_2O \) and electrolytes. The changes in vessel wall sodium, water and...
perhaps potassium associated with hypertension, have stimulated many to consider their role in the etiology of hypertension. Table 1 is a summary tabulation of reports made by several investigators. Data are still scarce; the species and type of hypertension as well as the analytical methods differ among the studies which have been reported. All who have measured the water content of arteries have found that it is increased in hypertension. Most investigators have found an increase in sodium; however, the changes observed in chloride and potassium have been variable. Unfortunately, most studies were limited to one or, at most, a few segments of the arterial tree. Our studies have shown that, in dogs, the electrolyte and water content and concentrations vary consistently along the arterial tree.\(^{6,9}\) Table 2 is again a summary of normalized data which represent data from nonhypertensive animals and man.

It is important to have a much clearer picture of the water and electrolyte changes associated with hypertension. Water itself may cause many changes in the artery wall which will produce a stiffer wall with a resultant increased peripheral resistance. A thickened wall will cause a decreased radius and a decreased radius-wall thickness ratio. In addition, it must be considered that water, in association with cellular products, can form relatively stiff materials. Electrolyte changes, as stated above, may also affect contractile properties of vascular smooth muscle which, in turn, result in further changes in vessel wall stiffness or tone.

The cause(s) of the changes in water and electrolyte content have not been explained.

---

### Table 1

<table>
<thead>
<tr>
<th>Species</th>
<th>% Changes in Dry Solids</th>
<th>Artery</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>16.7 10.8 31 77</td>
<td>Aorta</td>
<td>Tobian(^{\ast})</td>
</tr>
<tr>
<td>Rat (Renal)</td>
<td>10.0 42.1 0.0</td>
<td>Aorta</td>
<td>Tobian(^{\ast})</td>
</tr>
<tr>
<td>9.7 15.4 10.0 2.5</td>
<td>Aorta</td>
<td>Tobian(^{\ast})</td>
<td></td>
</tr>
<tr>
<td>7.6 5.6 15.0</td>
<td>Mesentery</td>
<td>Tobian(^{\ast})</td>
<td></td>
</tr>
<tr>
<td>18.6 13.2 14.5</td>
<td>Aorta</td>
<td>Daniel(^{\ast})</td>
<td></td>
</tr>
<tr>
<td>2.6 12.2</td>
<td>Aorta</td>
<td>Freed(^{\ast})</td>
<td></td>
</tr>
<tr>
<td>9.6 11.4 11.1</td>
<td>Aorta</td>
<td>Bondell (personal communication)</td>
<td></td>
</tr>
<tr>
<td>34.8 22.6 15.1 25.0</td>
<td>Mesentery</td>
<td>Koletsky(^{\ast})</td>
<td></td>
</tr>
<tr>
<td>Rat (DCA)</td>
<td>23.5 34.7 6.5</td>
<td>Aorta</td>
<td>Tobian(^{\ast})</td>
</tr>
<tr>
<td>4.8 9.1 0.0</td>
<td>Aorta</td>
<td>Tobian(^{\ast})</td>
<td></td>
</tr>
<tr>
<td>8.0 17.2 1.5</td>
<td>Aorta</td>
<td>Daniel(^{\ast})</td>
<td></td>
</tr>
<tr>
<td>10.3 1.0 13.6</td>
<td>Aorta</td>
<td>Gross(^{\ast})</td>
<td></td>
</tr>
<tr>
<td>4.3 13.3 6.6</td>
<td>Aorta</td>
<td>Bondell (personal communication)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{\ast}\)Changes of 5% are probably significant (p \(\approx\) .01); Changes of 10% are definitely significant (p \(\approx\) .001).
Average Normal Values*

<table>
<thead>
<tr>
<th>Species</th>
<th>Na (mEq/l 100 g dry solids)</th>
<th>K (mEq/l 100 g dry solids)</th>
<th>Cl (mEq/l 100 g dry solids)</th>
<th>Artery</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>75.0</td>
<td>13.5</td>
<td>18.4</td>
<td>Renal (M)</td>
<td>Tobian*</td>
</tr>
<tr>
<td>Rat</td>
<td>72.0</td>
<td>11.0</td>
<td>21.6</td>
<td>Aorta (M)</td>
<td>Tobian*</td>
</tr>
<tr>
<td></td>
<td>68.3</td>
<td>13.1</td>
<td>21.7</td>
<td>Aorta</td>
<td>Daniel*</td>
</tr>
<tr>
<td></td>
<td>65.8</td>
<td>15.6</td>
<td>20.8</td>
<td>Aorta</td>
<td>Gross*</td>
</tr>
<tr>
<td></td>
<td>62.9</td>
<td>11.1</td>
<td>27.8</td>
<td>Aorta</td>
<td>Freed*</td>
</tr>
<tr>
<td></td>
<td>60.4</td>
<td>10.8</td>
<td>32.7</td>
<td>Aorta</td>
<td>Randall (personal communication)</td>
</tr>
<tr>
<td></td>
<td>65.7</td>
<td>21.8</td>
<td>18.8</td>
<td>Mes. Art.</td>
<td>Tobian*</td>
</tr>
<tr>
<td></td>
<td>65.7</td>
<td>21.8</td>
<td>25.3</td>
<td>Mes. Art.</td>
<td>Tobian*</td>
</tr>
<tr>
<td>Rabbit</td>
<td>62.9</td>
<td>11.3</td>
<td>24.2</td>
<td>Aorta (3 mo.)</td>
<td>Waugh*</td>
</tr>
<tr>
<td></td>
<td>65.4</td>
<td>11.5</td>
<td>28.6</td>
<td>Aorta (6 mo.)</td>
<td>Waugh*</td>
</tr>
<tr>
<td>Dog</td>
<td>74.4</td>
<td>18.2</td>
<td>26.8</td>
<td>Aorta</td>
<td>Peterson et al*</td>
</tr>
<tr>
<td></td>
<td>73.7</td>
<td>18.6</td>
<td>25.8</td>
<td>Aorta</td>
<td>Peterson et al*</td>
</tr>
<tr>
<td></td>
<td>71.2</td>
<td>14.4</td>
<td>24.2</td>
<td>Aorta</td>
<td>Peterson et al*</td>
</tr>
<tr>
<td></td>
<td>72.0</td>
<td>12.1</td>
<td>25.6</td>
<td>Aorta</td>
<td>Peterson et al*</td>
</tr>
<tr>
<td></td>
<td>69.7</td>
<td>9.9</td>
<td>26.0</td>
<td>Femoral</td>
<td>Peterson et al*</td>
</tr>
<tr>
<td></td>
<td>71.2</td>
<td>10.0</td>
<td>27.0</td>
<td>Femoral</td>
<td>Tobian*</td>
</tr>
</tbody>
</table>

* Simplified summary to illustrate the general order of values for water and electrolytes found in the vessel walls of various species, in various sites, and by various authors. The column labeled Artery refers, as in table 1, to the site from which samples were obtained. Thus Renal (M) refers to the media of the renal artery; Mes. Art. refers to the 'arterioles' of the mesentery vessels; Aorta (3 mo.) refers to vessels obtained from 3-month-old animals.

One loop noted in figure 2, which has been said to affect water and electrolyte balance, includes the renin-angiotensin mechanism which stimulates the adrenal cortex to produce excessive aldosterone; the resultant effect on renal tubular mechanisms is an alteration of the excretion of water, sodium, potassium, and indirectly of other electrolytes.7 There is, however, no evidence, known to this author, that either the concentrations of sodium and potassium in the body’s fluid compartments which surround the vessel walls are altered in hypertension, or that the aldosterone-renal tubular mechanism alters the concentrations of those ions in the vessel wall. Thus, some other unknown mechanism(s) may be responsible for the hyperconcentration of electrolytes and for the increased water content.

Again, it may be germane to emphasize the feedback relationships of these loops to the mechanical properties of the vessel wall. The renin-angiotensin mechanism is presumably motivated by renal hemodynamic changes of an undefined nature; however, it is certain that they involve changes in the vessel walls which then affect the circulation within the kidney.

Thus, the blood vessels are affected by, and in turn affect, the nervous, endocrine and renal systems in a multiplicity of loops. As water and electrolyte changes in the vessel walls cause an increased stiffness, the electrical activity of the mecanoreceptors becomes altered with respect to blood pressure. This "resetting" of the receptor mechanisms and their relationship to the central nervous system are very poorly understood, but probably affect the efferent nervous and humoral mechanisms. Studies have been conducted in which the pressure within the carotid sinus, the carotid sinus wall strain and the electrical activity of the carotid sinus receptors have been recorded simultaneously.* These data have permitted the derivation of equations relating pressure, wall properties and recep-
tor activity of the carotid sinus receptor mechanism. Again, these equations are differential equations.

Unraveling of the mechanisms and of the etiology of hypertension, unless some unusual event of good fortune permits a decided short cut, will require the development of a "systems analysis" approach. This approach requires that as much knowledge of the interacting loops be assembled as possible, and that the boxes composing these loops be characterized as rigorously as possible. The approximated system is then programmed so that it can function as a simulation model of the real system. The simulated model can then be characterized and its character and responses to various stimuli can be compared to the real system. Comparisons between the behavior of the simulated and real systems make it possible to evaluate inadequacies in the present concepts of the control and regulation of the system. By such methods, it may be possible to determine further requirements for evaluating the black boxes and to predict the existence of missing loops. Furthermore, it is evident that almost none of the factors which constitute the loops have been evaluated sufficiently to permit characterization of the system. It is not surprising that apparently promising clues turn out to be disappointing and to become lost in the system.

Indeed, medical science has a great challenge in learning to apply the analytical tools that are already available and are rapidly developing. While it is still important to study isolated and limited variable systems, this will not suffice to comprehend the properties and behavior of the interactions of these individual systems. Not only is hypertension an example of this problem, but it must be admitted that we have explained very few of the body's systems responses, such as exercise, "shock," congestive failure, etc.

Summary
A major challenge to those investigating the etiology and progress of hypertension, as well as of other diseases, results from the fact that the control and regulation of most bodily functions are comprised of multiple feedback loops involving many bodily "systems."

Thus, mechanisms which seem to offer clues as to the etiology of an abnormality, when investigated as an isolated function, fail to explain the etiology when sought in the intact experimental animal or patient. Examples of simple closed-loop systems are described to illustrate the effects of feedback. A simplified diagram of several factors known to play a role in the control and regulation of the characteristics of the blood vessel wall is described to illustrate the multiplicity of the feedback pattern which probably occurs. Furthermore, it is evident that almost none of the factors which constitute the loops have been evaluated sufficiently to permit characterization of the system. It is not surprising that apparently promising clues turn out to be disappointing and to become lost in the system.

The medical investigator must learn to deal with methods of analyzing systems containing multiple factors and functions as well as to characterize the properties and behavior of the parts of the system.

Acknowledgment
The author wishes to acknowledge the advice and information supplied by Paul A. Rondell of the University of Michigan, and Allan W. Jones of the University of Pennsylvania, in assembling, summarizing and interpreting the information contained in tables 1 and 2.

References
7. Hypertension—Chemical and Hormonal Factors:
Dr. Walter M. Kirchendall, Iowa City, Iowa:

I think it most appropriate that Dr. Peterson should dwell on the relationships between the multiple factors which alter and affect blood pressure. The importance of such relationships can often be seen when one notices readjustments following drug administration. An alternation of the usual relationships among blood flow, blood pressure, and pulse rate was observed after chlorothiazide administration by Feisal and his associates1 at the Cardiovascular Research Laboratories of the State University of Iowa. They studied forearm vascular responses to norepinephrine in normal subjects before and during chronic administration of chlorothiazide. Before giving chlorothiazide, increasing doses of norepinephrine were associated with progressive decreases in forearm blood flow. During treatment with chlorothiazide, increasing doses of norepinephrine were associated with progressive increases in flow. Before chlorothiazide, the increases in blood pressure with norepinephrine were associated with progressive decreases in heart rate; during treatment, similar increases in blood pressure caused only small and inconsistent changes in rate. Drs. Eckstein, Abboud and Pereda2 carried out similar experiments in lightly anesthetized dogs; cardiac output was measured instead of extremity flow. Before chlorothiazide, norepinephrine caused slight decreases in cardiac output, appreciable increases in blood pressure, and decreases in heart rate. During treatment, norepinephrine caused distinct increases in cardiac output.
similar increases in blood pressure, but only small decreases in heart rate. Increases in forearm flow and cardiac output with nor-epinephrine during thiazide treatment along with failure of the normal decrease in heart rate as blood pressure increased, suggest that chlorothiazide in some way decreases the sensi-itivity of vagal-mediated, cardio-regulatory reflexes. Such an explanation might fit well with Dr. Peterson’s concepts, since it might be assumed that a decrease in body or regional sodium content might alter the feed-back sys-tem. Such observations make us realize that drugs which we think have primary effects on peripheral mechanisms actually may have an important part of their action contributed by a change in autonomic regulation. Finally, I should like to ask Dr. Peterson if he has measured the traffic over the autonomic nerves involved in cardio-regulatory reflexes in salt-depleted animals or in animals which have received a thiazide diuretic?

Dr. Harold D. Green, Winston-Salem, North Carolina: Many of us have been talking about resistance to flow for a number of years. Is not resistance to flow a transfer function? Cannot the pressure drop across a vascular bed be defined as an “output” for a system which would occur for a given rate of flow through the system which would be defined as the “input” to the system? I am relieved to hear Dr. Peterson point out that the engi-neers cannot really write these various com-plicated equations until they know how each individual system behaves in terms of its re-sponse to various applied stresses, and that no system in a complex unit can behave any differently from anything we can find in the individual behavior of the isolated system. On the other hand, it does behoove us to pay very close attention to what engineering con-cepts can teach us, because such concepts may force us to look for relationships in individual isolated organs which we never would have dreamed were present without the stim ulus from our engineering friends.

Dr. Edward D. Freis, Washington, D. C.: Dr. Peterson stressed the mechanical function of the arteries, that is, the stiffness of the arteries, as being important in the pathogene-sis of hypertension. I had always thought it was the geometrical properties or the radius changes which are important. I realize that loss of distensibility would be important but this is usually compensated for in hyperten-sives by an increase in the diameter and length of the large arteries.

Dr. Sydney M. Friedman, Vancouver: I am very pleased to hear Dr. Peterson speak this way about the multifactorial nature of the systems involved and the fact that in try-ing to decide how they work we must have basic information concerning the individual portions of that system. My only complaint about his figure 2 was that perhaps he under-estimated the complexity of the situation. Water and electrolytes were grouped together as just one entity, and of course one could re-do figure 2 and use water and electrolytes as the whole chart. Over the past couple of years, I have been trying to construct an analogue for the expected exchange of salt and water across two compartmental systems, such as might occur with the cells of the blood vessel. Each time I come close to a possible solution, I find that I have not enough equa-tions to work with because the basic data are lacking. Because of this, I think much of the caution Dr. Peterson has put before us must be taken quite seriously and I think that in accumulating the basic data, the choice of the preparation becomes extremely important. For example, I have at various times com-plained about the lack of applicability to the derivation of basic data of the aorta strip technique compared with whole amounts. I think this is quite important. Physiologically, the blood vessel operates against an intra-luminal pressure. It does not operate ob-liquely. One can derive a lot of information from a strip but one must not transpose it directly to the blood vessel without determining that this is valid. It is the same with the choice of the blood vessels themselves. We have been quite concerned with this, and
after prolonged study, Dr. Hinke has decided to use rat-tail arteries. These can be dissected; they measure about ½ mm in diameter, are largely muscular, and conform to what we describe as arteriolar in nature. Using such vessels in vitro, or a rat-tail perfusion system in vivo, we hope to obtain some basic data. If we are not to bog down in complexity, we must obtain really important basic data. Tables 1 and 2, which Dr. Peterson showed us, concerning quantities of salt and water in vessels disturbed me because I feel that in basic physical chemical terms, the actual amounts are quite unimportant. The distribution is what counts, as well as the relation of salt to water, and in this area there is almost no information whatsoever.

Dr. Lysle H. Peterson, Philadelphia: Figure 2 was simply an attempt to put some of the major present-day considerations down in what I agree is an overly simplified diagram. The purpose was to indicate that we are dealing essentially with a large number of loops, all of which probably involve some degree of feedback and also, to some degree, could be represented by differential equations. In other words, the changes are changes with respect to time, as well as to magnitude. I think we can at the present time write the equations and put them into the program for computer which will program the mechano-receptors. I think we can do it now for the carotid sinus. The properties of the receptors here are similar to the receptors elsewhere. A great deal more work has to be done in this area simply to find the functional relationship. I apologize to Dr. Green for using the term, transfer function. I do not know that it is necessarily an engineering term, but it is convenient to indicate the relationship between these variables. While I agree with Dr. Friedman that the water and electrolytes are lumped here, the effects of these are highly complex and probably also involve more than sodium and potassium. They may well involve calcium and other ions, and certainly the binding of water by sodium, potassium, calcium and other ions is very different. We really do not know the effects of these on mechanical properties; a number of workers during the past few years have shown that the electrolyte content of the artery wall affects the activity of the vascular smooth muscle. Since we are dealing with multiple loops in the system which controls blood pressure, if we consider one of these and it is involved in any sort of loop with feedback, the simplest possible relationship is one in which these two loops are considered together and not separately. Again, the slightest change will affect the input/output relationship, even though there may not be any particular change in this relationship at all. These could go from zero to infinity, with relatively slight changes in either of these together. It must be re-emphasized that if input/output—or any relationship—is a function of the rate at which it happens, this must also be considered. Otherwise, one simply cannot define what the function of A is. I am sure we would all agree that those very valuable clues, such as renin, angiotensin and the resetting of the carotid sinus or other mechanisms, will continue to elude us in their relationship to actual existing hypertension until they can be characterized. It is an axiom that the number of equations must be the same as that of the variables in order to determine the functional relationships of the variables. I agree with Dr. Green that resistance can be expressed as a transfer function. The real problem is to find out what changes the resistance, and this involves innumerable other transfer functions. Time does not permit full comment on Dr. Freis’ question as to the difference between the mechanical and geometric properties; they go hand in hand and are interrelated.

References
Systems Behavior, Feed-back Loops, and High Blood Pressure Research
LYSLE H. PETERSON
The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circres.ahajournals.org/content/12/5/585

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/